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ORIGINAL PAPER

Theory of long distance interaction between antibodies and antigens

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Abstract Measuring the kinetics of antigen-antibody bindings we found an unexpected effect that can be explained by an automatic long distance detection of antigens by antibodies over up to 2 mm. We have developed a theory based on phase locking of THz waves, which leads antibodies automatically to their antigens. A mathematical proof of principle is done.

Keywords Antigen-antibody binding · Protein kinetics · Long distance force · THz waves · Immunogenicity

Unexpected kinetics of antigen-antibody bindings

In the research project ANDREA-Quant[1] we made measurements with the prototype of a submonolayer ellipsometer.[2] The clean surface of a silicon wafer was cleaned with hydrofluoric acid (HF) to remove the natural SiO_2 layer. Then recombinant ARA H2 antigens (peanut allergy) of the same size were coupled without chemicals directly to the silicon surface. In air we measured an antigen layer thickness of about 1 nm; in liquid the thickness increased to 2.71 nm. The antigen-covered silicon target was put into a 1 ml cell for making measurements. Human antibodies (IgE) were put into the cell, and the binding was measured directly without labeling of the antibodies. Figure 1 shows the measured binding kinetic. If the binding were a stochastic effect as expected from classical binding theory, we would expect a binding characteristic as shown in the curve (1). But this model does not fit the measured binding kinetic. Assuming that there is a long distance force that gives a binding command to all antibodies within a defined reach from the antigens, we would have a kinetic that is defined by a straight line (2a) followed by an exponential binding characteristic (2b) as simulated by the black curve, which fits the measured kinetic (gray curve) very well. The same behavior was found for recombinant ARA H6 antigens (peanut allergy) and their antibodies, and for anti-myeloperoxidase autoantibodies (IgG and IgM of an autoimmune disorder) and their antigens. The measured linear binding kinetics can't be an artifact caused by measurement; it must be a systematic effect produced by the antibody-antigen interaction, because each single component of the ellipsometer was checked.

The submonolayer ellipsometer used for the measurements has an error corrected step motor with 360,000 steps per rotation (Kloppenburg and Riß 1992) and works with a stepping rate of 720,000 steps/s. The errors are measured in the complete 360° range with an angular encoder (Type RON, Heidenhain), contact free, in an optical box (a HeNe-laser beam is used as optical coupling between the motor and encoder, so that no mechanical moment exists between

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[1] The Andrea-Quant project was a project in cooperation with W.-M. Becker (clinical diagnostics, Research Center Borstel, Germany). The aim of this project was to create a new type of unfailing diagnostics. The recombinant ARA-H2 and ARA-H6 antigens used in this project were produced by the research group of W.-M. Becker. The project was sponsored by Technologiestiftung Schleswig-Holstein.

[2] The ellipsometer used was developed especially for this project by DRE-Dr. Riss Ellipsometerbau GmbH, Feldstr. 14, 23909 Ratzeburg, Germany. The submonolayer ellipsometer technique was honored in 1995 with the Schmidt-Römhild Technology Award for being the first technique able to measure submonolayers correctly. The experience with the ellipsometer described in this paper led to the development of the Enhanced EL X-02B III Ellipsometer, which already has software for up to five overlapping binding curves and special simulation software for calculating submonolayer mixtures. Contact address: dr.riss@dre.de.

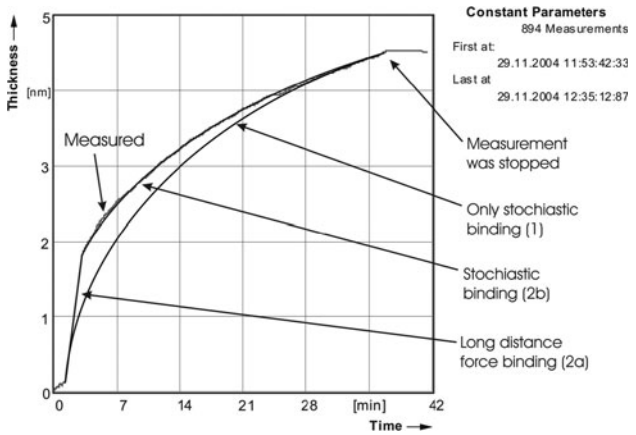

Fig. 1 Binding kinetic of human antibodies to recombinant ARA H2-antigens

the step motor and angle encoder). To increase the precision of the encoder, the internal coupling of the encoder was error corrected. The step motor errors measured with this system were stored in a file that is used by the instrument for error correction. After correction the step motor has a long time precision of ±0.002°. Heating the motor by 40 Kelvin reduces precision to ±0.003°. All measured data of the ellipsometer are based on the precision of this step motor. No calibration standards are needed for error correction or linearization. The instrument's detector has a dynamic range of 1:4,000,000. The only variable values for a calibration are the 0° reference plane and the polarization of the incident laser beam. The 0°-plane definition is prepared by aligning a horizontal plane with the laser beam and a quadrant diode in the detector. With an angle of incidence of 70°, the laser beam hits a plane silicon sample, so that the reflected beam hits the quadrant diode in the detector. The alignment table with the silicon sample can now be aligned with a precision of 0.001° to the plane, which is orthogonal to the plane spanned by the laser beam. Then a polarizing prism with a measured extinction ratio of 2.3×10^{-7} is put on the silicon sample, and the angle of incidence is changed to the transmission mode (angle of incidence: 90°). The polarization is measured. Taking the angle error of the prism into account, this measurement defines the −45° orientation. From this the 0°-orientation is calculated for the step motor. In the next step the polarization of the incident light is measured directly without a prism in transmission mode. This value is also stored and will be used when measuring samples. All measurement data are related to absolute physical quantities. This makes the instrument independent of sample types. Reference samples are only used for checking whether this method works or not. Relevant for possible errors is the long-term stability of the step motor. The submonolayer ellipsometer accepts a measured value only after two internal measurements have given the same result. This is part of an internal procedure to measure intensity minima with 0.001° reproducibility (±0.002° error). Several institutions and companies have checked the instrument type very intensively.[3]

A possible error source for the measurements is the cell in which the binding kinetics was measured. Glass windows always show optical anisotropy, which influences the measurement result. The transmission behavior of the glass windows can be described by four optical transmission ellipsometric quantities, Δ, Ψ, φ and ρ (Holzapfel and Riss 1987; Riss and Holzapfel 1988). To get correct results, it is a must to make an error correction. The required error correction function had already been implemented in the software of the ellipsometer, so this error source had no influence on the results. To be sure that the measured kinetics is not caused by a measurement error artifact, we simulated the influence of possible errors on the measured kinetics (the ellipsometer is equipped with software that makes this error simulation possible), but we did not find any error source that could explain the measured kinetics.

After reducing the cell volume from 1 ml to 0.02 ml, the cell had only a small thickness so that the distance of each antibody to the surface with antigens was 2 mm or less. In this cell we found only a straight line as binding kinetics. The binding stopped abruptly, which was not expected from classical binding theory. This only makes sense if the long distance interaction has a reach of 2 mm or more. From this we concluded that the reach of the long distance force can be 2 mm or more.

However, we found this long distance force only for unlabeled antibodies; it was not measured for labeled antibodies. Figure 2 shows the binding characteristics of ARA H2 anti-antibodies with bound 40-nm gold particles to human ARA H2 antibodies. In this case the binding can be explained by the classical theory of stochastic binding. This measurement was started only 1 min after the measurement shown in Fig. 1 was stopped. Therefore, we are sure that the ellipsometer was working under the same conditions as for the first measurements (Fig. 1).

[3] Several institutions and companies have made tests with the ellipsometer.

The following tests have been made:

1. The instrument was tested with a large number of standard reference wafers (SiO_2/Si) in the thickness range 10–200 nm.
2. One to 20 cellulose monolayers (0.6 nm monolayer thickness) were put on a silicon wafer to check the linearity in the thickness range 0–12 nm.
3. Cellulose monolayers were put on a glass surface to check the refractive index of cellulose.
4. The native SiO_2 layer of a pure Si wafer was removed, and the kinetics of the oxidation process (0.7 nm in 1 h) was compared with the expected theoretical behavior.

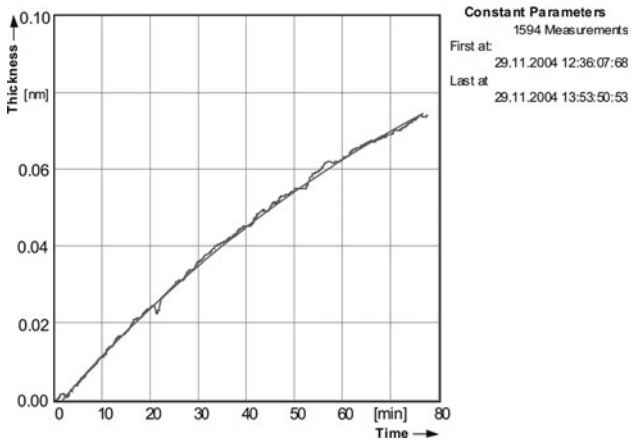

Fig. 2 Binding kinetics of gold-labeled anti-antibodies to human ARA H2 antibodies

To check our measurements with a second method, the sample was taken and analyzed with an atomic force microscope (AFM). The 40-nm gold particles can be seen very well with this type of instrument. We found seven gold particles in an area of 2.5 µm × 2.5 µm, which is absolutely consistent with data measured with the ellipsometer.

We found that there is a systematic difference in binding kinetics between labeled und unlabeled antibodies. Unlabeled antibodies bind significantly faster, and they have linear binding kinetics. Labeled antibodies show exponential binding kinetics as expected from the classical theory of stochastic binding. This reproducible behavior can be explained by a long distance force that only exists for unlabeled antibodies. Figure 3 shows how our measured data can be interpreted.

All unlabeled antibodies within a communication reach will get the command to swim to the antigen at the same time. This leads to a linear binding characteristic if the antibodies are equally distributed in the solution as start condition. All antibodies that get the command to swim to the antigens will move with the same speed to the antigen, independent of their distance from the antigens. All antibodies outside of the communication reach will act stochastically. In contrast to unlabeled antibodies, labeled antibodies have a stochastic binding behavior. They are not able to swim with constant speed to the antigen.

For labeled antibodies, we get a binding kinetic that can be described by:[4]

$$T(t) = \frac{1}{\gamma}\int_0^t \left(\frac{k_D[k_a(\Gamma_{\max} - \Gamma(t)) \cdot c_0 - k_d\Gamma(t)]}{k_a(\Gamma_{\max} - \Gamma(t)) + k_D}\right)\mathrm{d}t \qquad (1)$$

with $T(t)$: layer thickness in dependence of time, k_D: diffusion rate constant, k_a: association constant, k_d: dissociation constant, $\Gamma_{\max}$: maximal load of surface, $\Gamma(t)$: actual load of surface, c_0: start concentration and γ: specific weight.

For unlabeled antibodies we get:

$$T(t) = k_l \cdot t \quad \{t \leq t_0\}$$

$$T(t) = k_l \cdot t_0 + \frac{1}{\gamma}\int_{t_0}^t \left(\frac{k_D[k_a(\Gamma_{\max} - \Gamma(t)) \cdot c_0 - k_d\Gamma(t)]}{k_a(\Gamma_{\max} - \Gamma(t)) + k_D}\right)\mathrm{d}t \quad \{t > t_0\} \qquad (2)$$

k_l is a linear binding constant, and t_0 is the time in which all antibodies that are in the communication reach are bound to the antigens.

For the time range ($0 \leq t \leq t_0$) or, in other words, within the communication reach, binding of unlabeled molecules cannot be described by an affinity constant. We found that all unlabeled molecules that are in the communication reach are binding, which was not expected! This means, if there is only one antibody within the communication reach of the antigen, it will move to the antigen and bind.

The following is already known from proteins:

- Proteins have local electrical charges
- Proteins show THz oscillations that have an influence on surrounding water molecules

It is known that the electrical charges (coulomb forces) of proteins are able to influence the binding process if the distance to the target molecule is less than 2 nm (Pellegrini and Doniach 1993). But static coulomb forces are not big enough to bring a molecule to its target over a distance of 2 mm. By use of terahertz spectroscopy, it was shown that proteins oscillate with frequencies in the terahertz frequency range (Gruebele et al. 2008; 2010; Ebbinghaus et al. 2010). It is also known that this oscillation brings water molecules to systematic oscillation.

So we created a theory for antigen-antibody interaction that is able to explain the mechanisms of long distance detection of antigens by antibodies.

For better understanding, this theoretical model is split into the following components:

1. Mass-spring model of an antibody
2. Mathematical proof of phase locking of electric THz fields
3. Calculation of oscillation
4. Synchronous rotation of the antibody

[4] This equation comes from E-learning units of FIZ Chemie GmbH. The in this E-learning unit described quantity $\frac{\partial\Gamma(t)}{\partial t}$ is transformed to thickness information via $T(t) = \frac{1}{\gamma}\int_0^t \frac{\partial\Gamma(t)}{\partial t}\mathrm{d}t$ http://www.chemgapedia.de/vsengine/vlu/vsc/de/ch/13/vlu/kinetik/affinitaet/affinitaetsreaktionen.vlu/Page/vsc/de/ch/13/pc/kinetik/affinitaet/massentransp1.vscml.html.

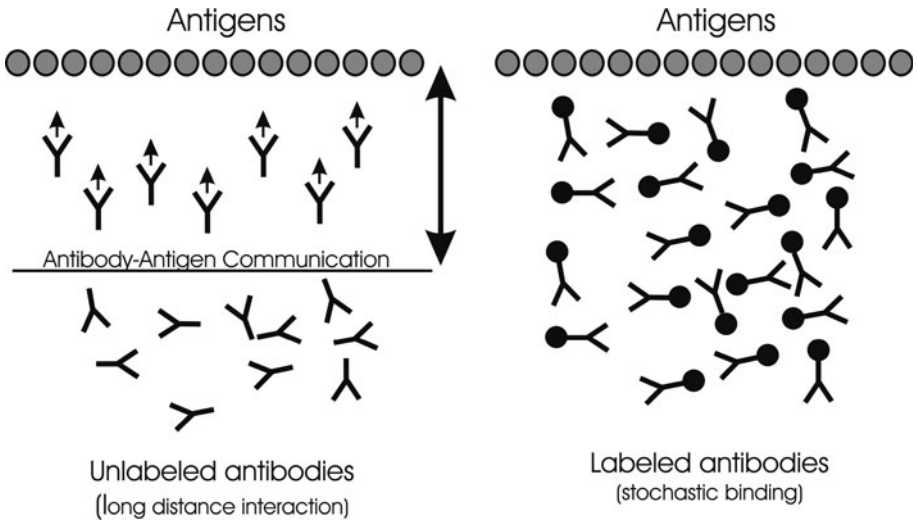

Fig. 3 Difference between unlabeled and labeled antibodies

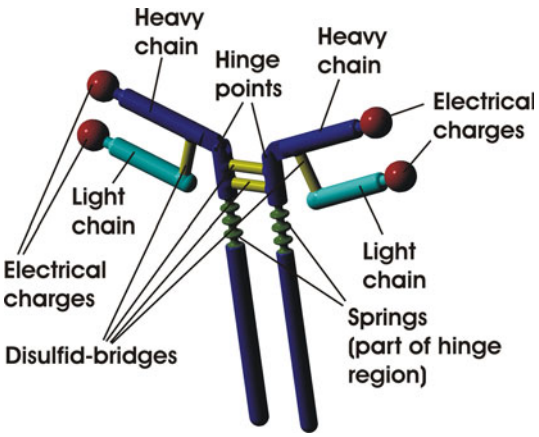

Fig. 4 Mass-spring model of an antibody

5. Effect of the moment of inertia
6. Required molecular size of oscillators

Mass-spring model of an antibody

Figure 4 shows our model of an antibody based on the real molecular structure of an antibody. We have only made simplifications.

The electrical charges are oscillating like a tuning fork in phase. There is an electrical coupling of both antibody arm oscillators. This electric coupling is reduced by the springs so that the system can detect an external oscillator. Otherwise, the electric coupling would be too strong for detecting external electric fields. The springs are located in the elastic hinge region of a real antibody. In two steps we simplified this model (Fig. 4) to the simplified model shown in Fig. 5.

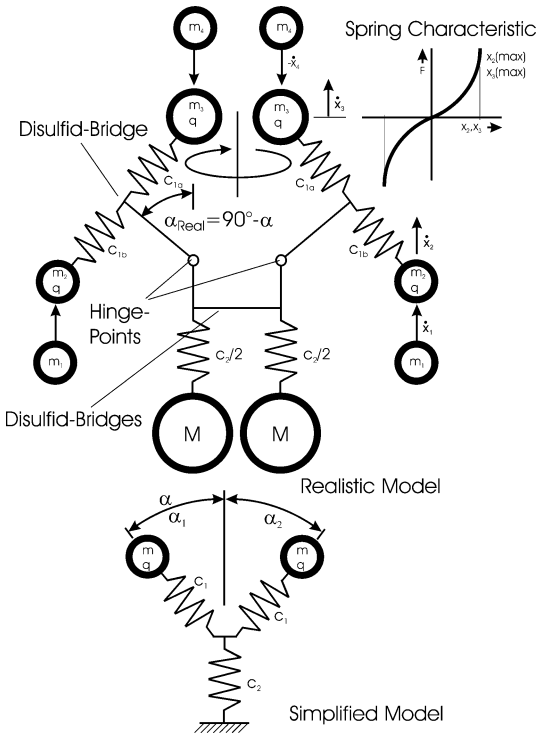

Fig. 5 Simplified mass-spring model of an antibody. m: mass, m_1, m_2: mass of parts in liquid (Brownian movement), m_3: mass of heavy chain, m_2: mass of light chain, M: mass of rest of antibody, q: electrical charge, c_1, c_2, c_{1a}, c_{1b}: spring constants, α_{Real}: arm angle of the realistic model, α: arm angle (both arms have same angle), α_1, α_2: arm angles (both arms have different angles)

The realistic model in Fig. 5 enables two oscillation frequencies per antibody. Real antibodies can have more arm oscillators, each disulfide bridge can be, but must not be the basis for an oscillator. The antibody is permanently supplied with energy by hits from parts *(m_1, m_4)* that are part of Brownian movement. The principle of energy

supply is described in Appendix 1. The hits of parts from Brownian movement are driving the antibody. An antibody with a heavy and light chain always has a forward movement in the direction of the heavy chains (m_3). The physical principle is described in Appendix 2. Steering of the antibody is possible if the spring characteristic between the heavy and the light chain is progressive non-linear (Fig. 5). The forward movement is bigger for that antibody arm where the oscillation amplitude is smaller. The principle is explained in Appendix 3.

To avoid unwanted amplitude modulations, each frequency of an oscillator must be similar, harmonic or sub-harmonic to the other oscillator frequencies. The simplified model we used for calculation only has one frequency. This simplified model is used for the mathematical proof of principle. It should be noted that the sides of the simplified model are exchanged compared to the realistic model and that the arm angles have the relationship: $\alpha_{\text{Real}} = 90° - \alpha$. This means the right side of the simplified model corresponds with the left side of the realistic model.

Mathematical proof of phase locking of electric THz fields

Compared to the realistic model (Fig. 5), it is very simple to calculate this simplified model. Figure 6 shows all quantities that are necessary for the calculation.

For the interaction force F_0 between the two oscillating masses of the antibody, we get:

$$F_0 = -F_0(G) + F_0(E) = \frac{-G_{\text{corr}} \cdot m^2 + k_{\text{corr}} \cdot q^2}{D^2} \tag{3}$$

with $F_0(G)$: Gravitation force, $F_0(E)$: Coulomb force, m: Mass, q: Electrical charge, D: Optical distance.

$$G_{\text{corr}} = G \cdot n_{\text{THz}}$$

$$G = 6.67428 \cdot 10^{-11} \frac{\text{Nm}^2}{\text{kg}^2}$$

$$k_{\text{corr}} = k_e \cdot e^{-k_{\text{THz}}}$$

$$k_e = 8.987551787 \cdot 10^9 \frac{\text{Nm}^2}{C}$$

n_{THz}: Real part of refractive index of the ambient medium; k_{THz}: imaginary part of refractive index of the ambient medium.

The gravitation force component $F_0(G)$ and the coulomb force component $F_0(E)$ have different directions.

After splitting the force F_0 in components in x_1 and x_2 direction, we get for the forces $F_0(x_1)$ and $F_0(x_2)$:

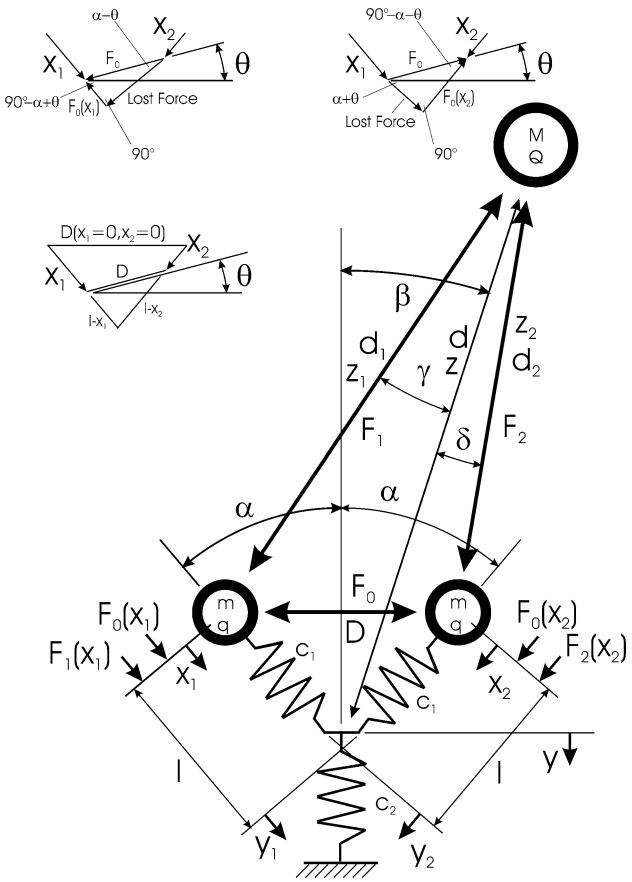

Fig. 6 Definition of quantities for the simplified antibody model. With x_1: Position in direction of oscillation; x_2: position in direction of oscillation; y_1: position in direction of oscillation (used for equation of movement); y_2: position in direction of oscillation (used for equation of movement); y: position in direction of spring c_2 (used for equation of movement); c_1: spring constant; c_2: spring constant; F_0: interaction force of electrically charged oscillating masses of the antibody; $F_0(x_1)$: force component of F_0 in x_1 direction; $F_0(x_2)$: force component of F_0 in x_2 direction; F_1: interaction force of electrically charged oscillating masses of the antibody and antigen; F_2: interaction force of electrically charged oscillating masses of the antibody and antigen; $F_1(x_1)$: force component of F_1 in x_1 direction; F_2x_2): force component of F_2 in x_2 direction; m: mass of the oscillating component of the antibody; M: mass of the oscillating component of the antigen; q: electrical charge of antibody masses; Q: electrical charge of antigen mass; D: optical distance of electrically charged masses of the antibody; d: optical distance between antigen and antibody; d_1,d_2: optical distance between antigen mass and antibody mass; z: physical distance between antigen and antibody; z_1,z_2: physical distance between antigen mass and antibody mass; α: angle of the antibody arm; β: angle of the antigen mass; δ: angle between d and d_2; θ: angle related to force F_0; γ: angle between d and d_1; l: length of spring. Lost force is a force that is orthogonal to x_1 or x_2 and is not taken into account for calculation

$$F_0(x_1) = -F_0(\sin\alpha \cdot \cos\theta - \cos\alpha \cdot \sin\theta)$$
$$F_0(x_1) \approx -F_0 \cdot \sin\alpha + F_0 \cos\alpha \frac{x_1 - x_2}{2l \cdot \tan\alpha} \tag{4}$$

$$F_0(x_2) = -F_0(\sin\alpha \cdot \cos\theta + \cos\alpha \cdot \sin\theta)$$
$$F_0(x_2) \approx -F_0 \sin\alpha - F_0 \cos\alpha \frac{x_1 - x_2}{2l \cdot \tan\alpha} \quad (5)$$

For coupling of charges the differential quotients $\frac{\partial F_0(x_1)}{\partial x_2}$ and $\frac{\partial F_0(x_2)}{\partial x_1}$ are relevant. They can be calculated as:

$$\frac{\partial F_0(x_1)}{\partial x_2} \approx -2(n_{\mathrm{THz}})^2 \sin^3\alpha(2l - x_1 - x_2)\frac{(-G_{\mathrm{Corr}}m^2 + k_{\mathrm{corr}}q^2)}{D^4} - \cos\alpha\frac{(-G_{\mathrm{Corr}}m^2 + k_{\mathrm{corr}}q^2)}{2l \cdot \tan\alpha \cdot D^2} \quad (6)$$

$$\frac{\partial F_0(x_2)}{\partial x_1} \approx -2(n_{\mathrm{THz}})^2 \sin^3\alpha(2l - x_1 - x_2)\frac{(-G_{\mathrm{Corr}}m^2 + k_{\mathrm{corr}}q^2)}{D^4} - \cos\alpha\frac{(-G_{\mathrm{Corr}}m^2 + k_{\mathrm{corr}}q^2)}{2l \cdot \tan\alpha \cdot D^2} \quad (7)$$

It follows: $\frac{\partial F_0(x_1)}{\partial x_2} \approx \frac{\partial F_0(x_2)}{\partial x_1}$.

The complete mathematics for calculation of $\frac{\partial F_0(x_1)}{\partial x_2}$ and $\frac{\partial F_0(x_2)}{\partial x_1}$ are shown in Appendix 4.

The forces between antibody and antigen F_1, F_2 and their differential quotients $\frac{\partial F_1(x_1)}{\partial x_1}$ and $\frac{\partial F_2(x_2)}{\partial x_2}$ can also be calculated in a simple manner.

If the optical distance d to the antigen is long in relation to D, it can be simplified:

$$\gamma \approx 0^\circ$$
$$\delta \approx 0^\circ$$
$$d_1 = n_{\mathrm{THz}} \cdot z_1 \approx d_2 = n_{\mathrm{THz}} \cdot z_2 \approx d = n_{\mathrm{THz}} \cdot z$$
$$\frac{|F_1|}{F_1} = \frac{|F_2|}{F_2} \quad (8)$$

n_{THz}: Real part of the refractive index of the ambient medium.

Then we get for the forces F_1 and F_2 and the force components $F_1(x_1)$ and $F_2(x_2)$:

$$F_1 \approx \frac{-G_{\mathrm{corr}}M \cdot m + k_{\mathrm{corr}}Q \cdot q}{(d + x_1 \cdot n_{\mathrm{THz}}\cos\alpha)^2}$$
$$F_1(x_1) \approx \frac{-G_{\mathrm{corr}}M \cdot m + k_{\mathrm{corr}}Q \cdot q}{(d + x_1 \cdot n_{\mathrm{THz}}\cos\alpha)^2}\cos(\alpha + \gamma) \quad (9)$$

$$F_2 \approx \frac{-G_{\mathrm{corr}}M \cdot m + k_{\mathrm{corr}}Q \cdot q}{(d + x_2 \cdot n_{\mathrm{THz}}\cos\alpha)^2}$$
$$F_2(x_2) \approx \frac{-G_{\mathrm{corr}}M \cdot m + k_{\mathrm{corr}}Q \cdot q}{(d + x_2 \cdot n_{\mathrm{THz}}\cos\alpha)^2}\cos(\alpha - \gamma) \quad (10)$$

After differentiation we obtain from (9) and (10):

$$\frac{\partial F_1(x_1)}{\partial x_1} \approx \frac{-2n_{\mathrm{THz}}(-G_{\mathrm{corr}}M \cdot m + k_{\mathrm{corr}}Q \cdot q)\cos\alpha \cdot \cos(\alpha + \gamma)}{d^3} \quad (11)$$

$$\frac{\partial F_2(x_2)}{\partial x_2} \approx \frac{-2n_{\mathrm{THz}}(-G_{\mathrm{corr}}M \cdot m + k_{\mathrm{corr}} \cdot Q \cdot q)\cos\alpha \cdot \cos(\alpha - \gamma)}{d^3} \quad (12)$$

Appendix 5 shows the calculation of the differential quotients $\frac{\partial F_1(x_1)}{\partial x_1}$ and $\frac{\partial F_2(x_2)}{\partial x_2}$ with more details.

The equation of motion received from Fig. 6 gives:

$$m\ddot{x}_1 + c_1(x_1 - y_1) + c_2 y + \frac{\partial F_0(x_1)}{\partial x_2}x_2 + \frac{\partial F_1(x_1)}{\partial x_1}x_1 = 0$$

$$m\ddot{x}_2 + c_1(x_2 - y_2) + c_2 y + \frac{\partial F_0(x_2)}{\partial x_1}x_1 + \frac{\partial F_2(x_2)}{\partial x_2}x_2 = 0$$

with:

$$y = y_1\cos\alpha = y_2\cos\alpha$$
$$x_1 c_1\cos\alpha + x_2 c_1\cos\alpha = y c_2$$
$$y = \frac{c_1\cos\alpha}{c_2}(x_1 + x_2) \quad (13)$$

Important is that $\frac{\partial F_0(x_1)}{\partial x_2}$ and $\frac{\partial F_0(x_2)}{\partial x_1}$ are negative because $k_{\mathrm{corr}}q^2 \gg G_{\mathrm{corr}}m^2$. So the strong electrical coupling of the antibody arms is compensated for by spring c_2. This makes phase locking to external electromagnetic fields possible.

With the mathematical substitutions $x_1 = A_1 e^{\lambda t}$ and $x_2 = A_2 e^{\lambda t}$ we get from (13) the eigenvalue equation for λ:

$$\left(m\lambda^2 + \left[c_1\left(1 + \cos\alpha - \frac{c_1}{c_2}\right) + \frac{\partial F_1(x_1)}{\partial x_1}\right]\right) \cdot \left(m\lambda^2 + \left[c_1\left(1 + \cos\alpha - \frac{c_1}{c_2}\right) + \frac{\partial F_2(x_2)}{\partial x_2}\right]\right) - \left(c_1\left(\frac{c_1}{c_2} - \cos\alpha\right) - \frac{\partial F_0(x_2)}{\partial x_1}\right) \cdot \left(c_1\left(\frac{c_1}{c_2} - \cos\alpha\right) - \frac{\partial F_0(x_1)}{\partial x_2}\right) = 0 \quad (14)$$

How we obtained this equation is shown in Appendix 6.

With the simplifications $\gamma \approx 0^\circ$ and $\frac{\partial F_0(x_2)}{\partial x_1} = \frac{\partial F_0(x_1)}{\partial x_2}$ and the replacements:

$$
\begin{aligned}
k_1 &= c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right)+\frac{\partial F_1(x_1)}{\partial x_1}\\
&= c_1\left(1+\cos\alpha-\frac{c_1}{c_2}+\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1}\right)\\
k_2 &= c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right)+\frac{\partial F_2(x_2)}{\partial x_2}\\
&= c_1\left(1+\cos\alpha-\frac{c_1}{c_2}+\frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}\right)\\
k_3 &= c_1\left(\frac{c_1}{c_2}-\cos\alpha\right)-\frac{\partial F_0(x_2)}{\partial x_1}\\
&= c_1\left(\frac{c_1}{c_2}-\cos\alpha\right)-\frac{\partial F_0(x_1)}{\partial x_2}\\
k_3 &= c_1\left(\frac{c_1}{c_2}-\cos\alpha-\frac{\partial F_0(x_2)}{\partial x_1\cdot c_1}\right)\\
&= c_1\left(\frac{c_1}{c_2}-\cos\alpha-\frac{\partial F_0(x_1)}{\partial x_2\cdot c_1}\right)
\end{aligned}
\tag{15}
$$

we get the more compact eigenvalue equation from (14):

$$
\begin{aligned}
&\left(m\lambda^2+k_1\right)\cdot\left(m\lambda^2+k_2\right)-(k_3)^2=0\\
&\det(\bar{T})=\lambda^4+\frac{(k_1+k_2)}{m}\lambda^2+\frac{k_1k_2-(k_3)^2}{m^2}=0
\end{aligned}
\tag{16}
$$

This equation can be solved.

$$
\begin{aligned}
\Rightarrow\lambda_{1,2}^2 &= -\frac{(k_1+k_2)}{2m}\\
&\quad\pm\sqrt{\left(\frac{(k_1+k_2)}{2m}\right)^2-\frac{k_1k_2-(k_3)^2}{m^2}}\\
\Rightarrow\lambda_{1,2}^2 &= \frac{(-k_1-k_2)\pm\sqrt{(k_1)^2+2k_1k_2+(k_2)^2-4k_1k_2+4(k_3)^2}}{2m}\\
\Rightarrow\lambda_{1,2}^2 &= \frac{(-k_1-k_2)\pm\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2m}
\end{aligned}
\tag{17}
$$

The imaginary eigenvalues λ_i can be transferred to real angular frequencies ω_i. This is a commonly used method.

$$
\begin{aligned}
\lambda_1 &= \pm i\sqrt{\frac{(k_1+k_2)-\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2m}}\\
\lambda_2 &= \pm i\sqrt{\frac{(k_1+k_2)+\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2m}}\\
\omega_1 &= \sqrt{\frac{(k_1+k_2)-\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2m}}\\
\omega_2 &= \sqrt{\frac{(k_1+k_2)+\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2m}}
\end{aligned}
\tag{18}
$$

The coupled oscillator system has a terahertz angular main frequency that is $\frac{\omega_1+\omega_2}{2}$. This is the oscillation frequency of the charged masses. If phase locking has not taken place, oscillation energy moves from one antibody arm to the other, which creates an amplitude modulation with an angular frequency of $\frac{\omega_2-\omega_1}{2}$. If phase locking takes place the oscillator amplitudes are frozen ($\omega_1=\omega_2$); no amplitude modulation exists. Both oscillator arms are oscillating with frequency $\frac{\omega_1+\omega_2}{2}$ and both arm oscillators do not exchange energy. The frequency for energy exchange is now $\frac{\omega_2-\omega_1}{2}=0$ which should be defined as phase locking.

Now the boundary condition for phase locking is $\omega_1=\omega_2$. We get from (18):

$$
\begin{aligned}
k_1 &= k_2\\
k_3 &= 0
\end{aligned}
\tag{19}
$$

k_1, k_2 and k_3 are defined in (19). It follows for the boundary condition of phase locking from Eq. 14:

$$
\begin{aligned}
k_3 &= c_1\left(\frac{c_1}{c_2}-\cos\alpha-\frac{\partial F_0(x_2)}{\partial x_1\cdot c_1}\right)=0\\
&\Rightarrow\alpha=\arccos\left(\frac{c_1}{c_2}-\frac{\partial F_0(x_2)}{\partial x_1\cdot c_1}\right)\\
k_1 &= c_1\left(1+\cos\alpha-\frac{c_1}{c_2}+\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1}\right)=k_2\\
&= c_1\left(1+\cos\alpha-\frac{c_1}{c_2}+\frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}\right)\\
&\Rightarrow\frac{\partial F_1(x_1)}{\partial x_1}=\frac{\partial F_2(x_2)}{\partial x_2}
\end{aligned}
\tag{20}
$$

These equations can be solved, which means phase locking is possible if the antigen is straight ahead and the arm angle α can be moved. The arm angle position depends on the strength of the $\frac{\partial F_0(x_2)}{\partial x_1}$ signal.

The antibody arms must have different arm angles α_1 and α_2 if the antigen is not straight ahead. Instead of Eq. 15 we have now:

$$k_1 = c_1\left(1+\cos\alpha_1-\frac{c_1}{c_2}+\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1}\right)$$
$$k_2 = c_1\left(1+\cos\alpha_2-\frac{c_1}{c_2}+\frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}\right)$$
$$k_3 = c_1\sqrt{\left(\frac{c_1}{c_2}-\cos\alpha_1-\frac{\partial F_0(x_2)}{\partial x_1\cdot c_1}\right)\cdot\left(\frac{c_1}{c_2}-\cos\alpha_2-\frac{\partial F_0(x_1)}{\partial x_2\cdot c_1}\right)}$$

with:

$$\frac{\partial F_0(x_2)}{\partial x_1}\neq\frac{\partial F_0(x_1)}{\partial x_2} \tag{21}$$

The phase locking condition is now:

$$k_3 = c_1\sqrt{\left(\frac{c_1}{c_2}-\cos\alpha_1-\frac{\partial F_0(x_2)}{\partial x_1\cdot c_1}\right)\left(\frac{c_1}{c_2}-\cos\alpha_2\right)-\frac{\partial F_0(x_1)}{\partial x_2\cdot c_1}} = 0$$
$$\Rightarrow\cos\alpha_1 = \left(\frac{c_1}{c_2}-\frac{\partial F_0(x_2)}{\partial x_1\cdot c_1}\right)$$
$$\Rightarrow\cos\alpha_2 = \left(\frac{c_1}{c_2}-\frac{\partial F_0(x_1)}{\partial x_2\cdot c_1}\right)$$
$$k_1 = c_1\left(1+\cos\alpha_1-\frac{c_1}{c_2}+\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1}\right) = k_2$$
$$= c_1\left(1+\cos\alpha_2-\frac{c_1}{c_2}+\frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}\right)$$
$$\Rightarrow\cos\alpha_1-\cos\alpha_2 = \frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}-\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1}$$
$$\Rightarrow\frac{\partial F_0(x_1)}{\partial x_2\cdot c_1}-\frac{\partial F_0(x_2)}{\partial x_1\cdot c_1} = \frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}-\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1} \tag{22}$$

In this case phase locking of electric fields is also possible, but the angles α_1 and α_2 are different. Important is that $\frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}-\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1}$ depends on the angles α_1 and α_2, and the optical distance d to the antigen. From the point of mechanical closed loop control of the antibody, it makes sense that the quotients $\frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}$ and $\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1}$ are independent of the distance to the antigen. From (11) and (12) we now get for $\gamma\approx 0$:

$$\frac{\partial F_1(x_1)}{\partial x_1\cdot c_1}\approx\frac{-2n_{\mathrm{THz}}(-G_{\mathrm{corr}}M\cdot m+k_{\mathrm{corr}}Q\cdot q)\cos^2\alpha_2}{c_1\cdot d^3}$$
$$\frac{\partial F_2(x_2)}{\partial x_2\cdot c_1}\approx\frac{-2n_{\mathrm{THz}}(-G_{\mathrm{corr}}M\cdot m+k_{\mathrm{corr}}Q\cdot q)\cos^2\alpha_1}{c_1\cdot d^3} \tag{23}$$

To get independence from the distance d to the antigen, it should be:

$$\frac{\cos^2\alpha}{d^3}\approx\frac{\cos^2\alpha_1}{d^3}\approx\frac{\cos^2\alpha_2}{d^3}\approx\text{constant} \tag{24}$$

This is the case if the angle α (α_1, α_2) is adapted to the distance d. When the antibody moves to the antigen, the arm angle α (α_1, α_2) increases and the arm angle α_{Real} decreases. Directly before the antigen is reached the arm angle α (α_1, α_2) has its biggest value, which means that the angle α_{Real} of the real antibody has its smallest value. This makes the binding process easier, because the binding area of the antibody is brought to the antigen. Now static coulomb forces (Pellegrini and Doniach 1993) can influence the rest of the binding process.

So we can resume: On the way to the antigen, the antibody has information on the angle position of the antigen and the distance to the antigen. The long distance interaction reduces the distance between antibody and antigen, so that static coulomb forces [4] are able to influence the binding process. At least molecular forces are overtaking the binding process.

Calculation of oscillation

So far we have calculated the condition for phase locking, but the calculation of the oscillation equations also gives interesting information.

For the frequency ω_1, we get from the eigenvalue equation the following relevant relationships (see Appendix 7):

$$A_1 = -\frac{2k_3}{-k_1+k_2-\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}A_2$$

and

$$A_1 = -\frac{-k_2+k_1-\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2k_3}A_2 \tag{25}$$

and for the frequency ω_2 we have the following relationship:

$$A_1 = -\frac{2k_3}{-k_1+k_2+\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}A_2$$

and

$$\rightarrow A_1 = -\frac{-k_2+k_1+\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2k_3}A_2 \tag{26}$$

where A_1 and A_2 come from the mathematical substitutions $x_1 = A_1\cdot e^{\lambda t}$ and $x_2 = A_2\cdot e^{\lambda t}$.

In Eqs. 25 and 26 are two competing definitions for A_1. These two conditions are only identical for $(k_3)^2 = k_1k_2$ or $k_1 = k_2$. For us, $k_1 = k_2$ is relevant. For this case we get from (25) and (26) $A_1 = A_2$, which makes sense.

From the equation of motion 13 it can be seen that the possible amplitude modulation of both antibody arms is different ($k_1 \neq k_2$) before the hinge points are used to

fulfill the required condition $k_1 = k_2$. Before this condition is reached, the oscillator, which is nearer to the antigen, has higher possible amplitude, and energy is led into the movement of the arms. This leads to the use of the hinge points and the angular motion of the antibody arms until the condition $k_1 = k_2$ is fulfilled. The antibody is always moving the arms via the hinge points so that the antigen is located in the bisector of the angle $(\alpha_1 + \alpha_2)$, which is built by both antibody arms. The antibody arms are pulling the antibody body until it is also in the direction of the bisector.

The now following complete calculation is done for the case in which the antigen is straight ahead of the antibody, which is very similar to the case in which the antigen is in the direction of the bisector of the antibody arms.

For this case we get as possible solutions:

$$\begin{aligned} &x_1 = x_2 = A_1 \cdot e^{i\omega_1 t}, x_1 = x_2 = A_1 \cdot e^{-i\omega_1 t} \\ &x_1 = -x_2 = A_1 \cdot e^{i\omega_2 t}, x_1 = -x_2 = A_1 \cdot e^{-i\omega_2 t} \end{aligned} \tag{27}$$

The result of the differential equation is a combination of linear independent homogeneous results. We get:

$$\begin{aligned} &x_1 = C_1 \cdot e^{i\omega_1 t} + C_2 \cdot e^{-i\omega_1 t} + C_3 \cdot e^{i\omega_2 t} + C_4 \cdot e^{-i\omega_2 t} \\ &x_2 = C_1 \cdot e^{i\omega_1 t} + C_2 \cdot e^{-i\omega_1 t} - C_3 \cdot e^{i\omega_2 t} - C_4 \cdot e^{-i\omega_2 t} \\ &C_i \in C \end{aligned} \tag{28}$$

Using $e^{i\omega t} = \cos\omega t + j\sin\omega t, e^{-i\omega t} = \cos\omega t - j\sin\omega t$ we can calculate the oscillation of both oscillator arms with $A = A_1 = A_2$:

$$\begin{aligned} x_1 &= \frac{A}{2}(\cos(\omega_1 t + \phi_1) + \cos(\omega_2 t + \phi_2)) \\ x_1 &= \frac{A}{2}\left(\cos\left(\frac{(\omega_1 + \omega_2)t + \phi_1 + \phi_2}{2}\right)\right. \\ &\quad \left.\cos\left(\frac{(\omega_1 - \omega_2)t + (\phi_1 - \phi_2)}{2}\right)\right) \\ x_2 &= \frac{A}{2}(\cos(\omega_1 t + \phi_1) - \cos(\omega_2 t + \phi_2)) \\ x_2 &= -\frac{A}{2}\left(\sin\left(\frac{(\omega_1 + \omega_2)t + \phi_1 + \phi_2}{2}\right)\right. \\ &\quad \left.\sin\left(\frac{(\omega_1 - \omega_2)t + (\phi_1 - \phi_2)}{2}\right)\right) \end{aligned} \tag{29}$$

Appendix 8 shows the calculation with more details. In Eq. 29 it can be seen that both oscillators of the antibody arms have a phase difference of 90° and that there is a permanent energy transport from one oscillator arm to the other with the angular frequency $(\omega_1 - \omega_2)/2$. The oscillators are oscillating with the angular frequency $(\omega_1 + \omega_2)/2$. A negative frequency $(\omega_1 - \omega_2)/2$ can be interpreted as a change in the energy transport direction. For a closed loop regulation of the antibody arms is this an advantage that makes control of the antibody easier.

It can be seen from Eq. 29 and the appendices that there are four different cases of oscillation. Figure 7 shows these different cases. Case A represents the case that no antigen is detected or an antigen is straight ahead, but the signal is not strong enough for phase locking.

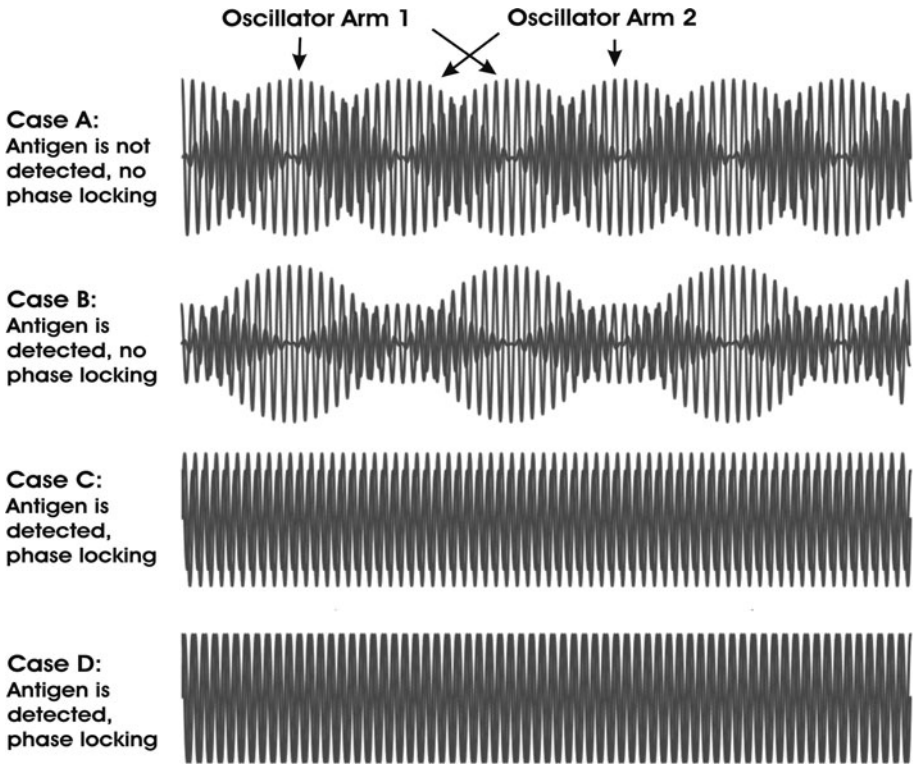

Fig. 7 Antibody oscillators identifying the presence of an antigen. *Case A*: No antigen is found. *Case B*: Antigen is found on bigger signal antibody arm side (signal is too low for phase locking, but hinge points are used). *Case C*: Antigen is found on bigger signal antibody arm side (signal is phase locked and hinge points are used). *Case D*: Antigen is found straight ahead (phase is locked)

Case B shows the case in which the antigen is close to the arm that is responsible for the bigger oscillation signal. In this case the signal is not strong enough for phase locking, but the signal is strong enough for starting an arm rotation around the hinge points to reach the required condition $k_1 = k_2$ (Please note: in this case Eq. 29 is not valid because $k_1 \neq k_2, A_1 \neq A_2$). After arm rotation has taken place $(\alpha_1 \neq \alpha_2), k_1 = k_2, A_1 = A_2)$ case A is reached again. In cases C and D phase locking has taken place. In case C the antigen is close to the arm that is responsible for the bigger oscillation signal; in Eq. 29 we have $\omega_1 - \omega_2 = 0$ and $k_3 = 0$. The different amplitudes of oscillation lead to further arm rotation around the hinge points, which means that the antibody is wobbling, to fulfill the conditions $k_1 = k_2$, $k_3 = 0$ until case D is reached (antigen is straight ahead of the antibody).

Synchronous rotation of the antibody

The phase locking model described above only works in 2D space, but it will lose phase locking if it is moving. Thus, there must be an additional mechanism that makes 3D detection of the antigen possible without losing phase. If the antibody is moving with speed $\dot{x}$ we get for the phase φ:

$$\varphi = \frac{\dot{x} \cdot t}{\lambda} 2\pi \tag{30}$$

with t: time, $\dot{x}$: speed of the antibody, λ: wavelength in the medium.

If the antibody is moving without rotation, the antibody must change its residual phase by changing its oscillation. This needs a lot of energy. But if the antibody is rotating synchronously to its speed, the phase can be changed without need of additional energy. In addition to this, the antibody is able to detect the antigen in the 3D space. Phase locking has the following requirements for rotation speed $\dot{\rho}$:

$$\dot{\rho} = \frac{2\pi \cdot \dot{x}}{\lambda} = \frac{4\pi^2 \cdot \dot{x} \cdot \omega}{n_{\mathrm{THz}} \cdot c} \tag{31}$$

with c: light speed, $\dot{x}$: speed of the antibody, λ: wavelength in the medium, n_{THz}: real part of the refractive index of the ambient medium, ω: angular frequency.

For rotation the light chains of the antibody need to be located at positions where they also produce a rotation movement of the antibody. Looking at the molecular structures of a real antibody[5] we found a structure that will produce in addition to a forward movement a rotation movement. Proteins are known to bring water molecules into the status of synchronous THz oscillation (Ebbinghaus et al. 2010). We think that the same mechanism is valid for antibodies. Assuming the case that the antigen is straight ahead, then the water molecules are oscillating in front of and behind the antibody arms. This leads to a local gradient of the wave front of oscillation, because the oscillation of both arms has a phase difference of 90°. The wave front of oscillation looks like a part of a screw winding (Fig. 8). And it acts like a screw winding. The phase shift of the wave front is the reason for the synchronous rotation of the antibody. Synchronous oscillation of the water molecules generates optimal power for the antibody movement.

There are some additional effects. The rotation of the antibodies stabilizes the movement of the antibodies over the gyroscope effect, and the oscillation of water increases the signal-to-noise ratio because water molecules are dipoles. Between antibody and antigen are many water dipoles oscillating in phase. Disturbing effects can have an influence on parts of this information channel between the antibody and antigen but have no influence on the complete system. If phase locking has taken place, then a small disturbing effect is healed by the inertia of oscillating elements. The disturbing effect must be put in relation to all oscillating elements (antigen, antibody arms and water dipoles). Therefore, it is relatively small.

If the distance between the antigen and antibody is less than the required minimal distance, the antibody detects the antigen and carries out phase locking. At first the antibody makes a wobbling movement until the antigen is straight ahead of the antibody arms (Fig. 9). Then a synchronous oscillation of the water molecule dipoles starts until a stable communication channel is installed between antibody and antigen. This stable communication can be interpreted as an extremely small AC current (alternating current) that oscillates in the THz frequency range. The arm angles of the antibody will be permanently adapted to the strength of the received signal.

In our experiment, energy for this in phase oscillation of water molecules comes mainly from the large number of antigens on the substrate. Water is a strong absorber for THz waves. Assuming an absorption coefficient of about 230 we calculate an intensity reduction of the signal of 10^{-20} and a reduction of the electrical field strength of 10^{-10} for an antigen-antibody distance of 2 mm. In our experiment we had a concentration of an expected 100,000–1700,000 antigens/μm^2 on the substrate. For a distance of 2 mm to the substrate, the antibody detects the combined electrical field from an antigen area of about 1 mm^2. In this area are about 10^{11}–1.7×10^{12} antigens that are interacting with the antibody. This large number of antigens creates a field that is stronger by a factor of 10^{11}–1.7×10^{12} than the field of a single antigen, and the field

[5] http://pathmicro.med.sc.edu/mayer/IgStruct2000.htm
Structure shown in rotating Fig. 2d (Fig. 2d rotates right handed for better viewing of the molecular structure; if moving to the antigen this molecule would rotate left handed according to our theory).

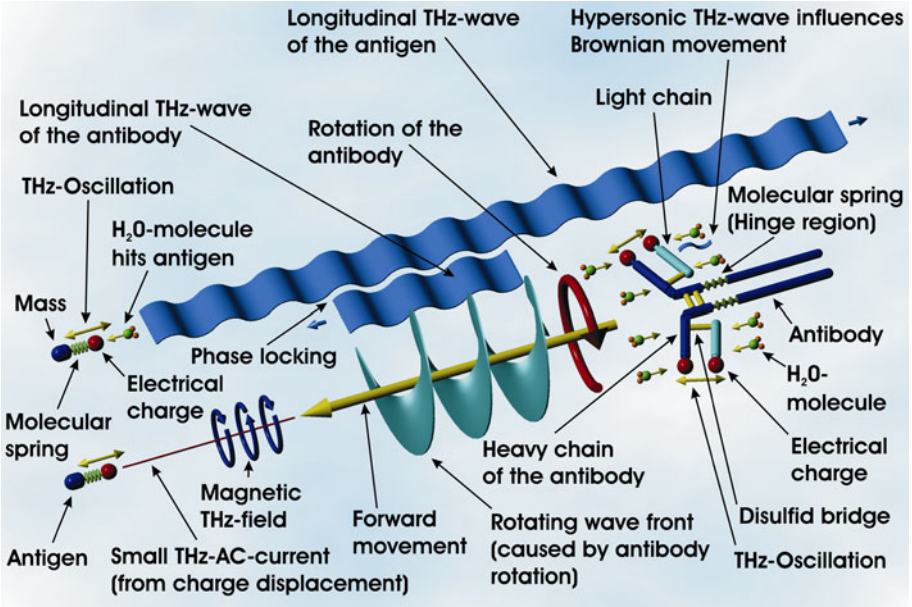

Fig. 8 Wave front of oscillation (principle without correct scaling)

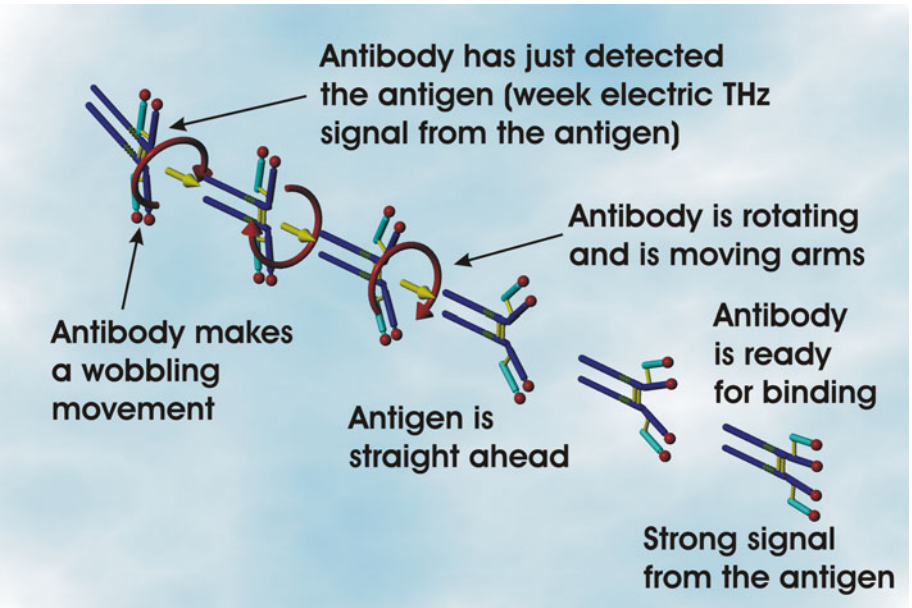

Fig. 9 Antibody movements after detecting an antigen

reduction of 10^{-10} will be totally compensated by the large number of antigens on the substrate. The antibody receives a strong electric THz signal.

For IgA and IgM antibodies it is also possible to construct a mechanism that shows a synchronous rotation for phase locking. In the case of IgA antibodies the rotation speed is half that of IgE, IgG or IgD antibodies (assuming the same oscillation frequency); in case of IgM antibodies, the rotation speed is reduced by a factor of five. The antibody rotation speed has a linear influence on the speed in the liquid. An IgG antibody moves five times faster than an IgM antibody (assuming the same oscillation frequency). However, IgA and IgM antibodies have larger moments of inertia as IgG antibodies, so they can transport a bigger load without losing synchronization.

Effect of the moment of inertia

Synchronous rotation of the antibody is only possible if the moment of inertia is not too big. If antibodies are labeled with a 40-nm gold particle as shown in Fig. 10, the moment of inertia increases significantly compared to the moment of inertia of the sole antibody.

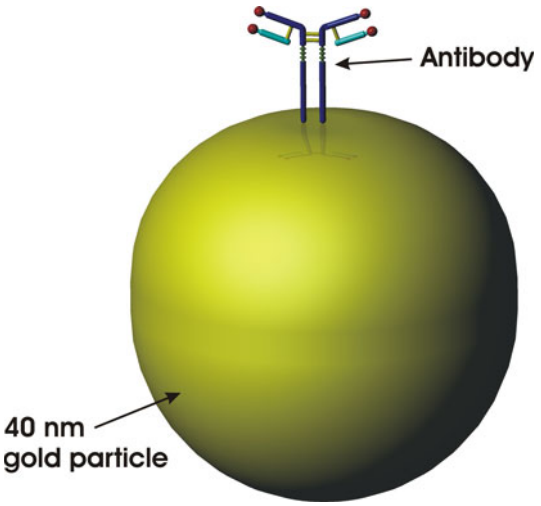

Fig. 10 Antibody with 40-nm gold particle. In reality the surface of the gold particle is covered with a large number of antibodies

The marked antibody is no longer able to rotate synchronously because the moment of inertia would require rotational forces that cannot be supplied by the antibody, and so the antibody loses phase locking. This leads to the binding characteristic shown in Fig. 2, which can be described by classical binding theory.

We assume that the rotation of antibodies is very sensitive to external loads. Even labeled antibodies with very small loads such as fluoresein tracers cannot be brought into phase locking condition, so the long distance interaction does not exist for this case.

Required molecular size of oscillators

The size of a molecular oscillator depends on the oscillation frequency. From Schoenauer et al. (2005) it can be calculated from the force-elongation diagram that spring constants between 2×10^{-4} and 8.6×10^{-3} N/m are found for real biomolecules with progressive spring characteristics. Bigger spring constants can be calculated from other force-elongation diagrams (Grandi et al. 2006). Here we found a spring constant of 3.5 N/m for K2, K3, K3 and K4 ANG domains, and 9×10^{9} N/m for an unfolded molecule. This shows that in reality a large range of spring constants exists. In general it can be said that folded molecules have a small spring constant, and unfolded molecules have a high spring constant (disulfide bridges must have a very high spring constant).

To realize an oscillation frequency of 1 THz, an antigen with a simple spring-mass system as oscillator can have for example an effective oscillating mass of 1,000 Da and a spring constant of 0.042 N/m (see Eq. 32).

$$f = \frac{1}{2\pi}\sqrt{\frac{c}{m}} \tag{32}$$

with f: frequency, c: spring constant, m: mass.

In an antibody arm larger masses are oscillating. We think each domain is a single spring-mass oscillator, and the arms (heavy and light chain connection) are designed as flexural resonators, where the oscillation frequency depends on the stiffness of the connecting disulfide bridge. A domain oscillator may have an effective oscillation mass of 12,000 Da. In that case the spring constant would be 0.5 N/m.

This example shows that our model makes sense even if the total masses of the antigen and antibody are totally different.

Conclusion

Biomolecules have an elastic structure and have a mass. They will start oscillating if hit by other molecules in a liquid. For calculation the well-known mathematics of technical mechanics can be transferred to the calculation of molecule oscillators.

A longitudinal electric THz field is created if the oscillating masses in the molecule are electrically charged. This is comparable with GHz oscillators, which are known from high frequency electronics. The required mathematics is well known for GHz high frequency and can also be used directly for calculation of the THz field.

Phase locking is also a well-known principle in high frequency techniques and optics. Therefore, the theory presented in this paper is based on well-known physics and mathematics. Only the application to antigens and antibodies is new. It is known that each system that consists of a mass and a spring starts oscillation if it is hit by other parts. The Brownian movement is defined as moving of parts. Therefore, they will hit the antigens, which lead to oscillation of the antigens. For oscillation in the THz frequency range the springs must have an adequate spring constant, which means that the antigens have a required minimal size for the required spring constants. It is commonly known that antigens that are too small show no immunogenicity. The minimal size of an antigen is in the range of 3.5 nm × 1 nm × 0.6 nm. This is large enough to create a spring with the required spring constant. Oscillation in the THz range is possible with this spring dimension. A longitudinal electric field will be created automatically if the oscillating mass is electrically charged. This electric field created by antigens is detected by antibodies that also have two or more electrically charged oscillators. To detect the electrical fields of antigens in the 3D space, the antibodies must rotate. If antibodies have

detected antigens, phase locking of electrical fields takes place, and they move with constant speed to the antigens. The antibodies move the arm angles via the hinge region on the way to the antigen. A second task of the hinge region is the compensation of the strong coupling of the electrically charged antibody arms so that external signals can be received. The oscillation of the antigens and the antibodies produces a charge displacement. If phase locking has taken place, there is a longitudinal wave between the antigen and antibody. This longitudinal wave can be interpreted as a small THz-AC current.

We think viruses use similar mechanisms to identify their targets. A virus has a big load. To make synchronous rotation with a big load possible, the rotational speed must be very slow. For a small rotational speed the surface of the load must have many coupled oscillators with a small phase shift between neighboring oscillators. With such a structure the virus rolls on the wave that is created by antigens. In this case antibodies that are docking on the virus have the task of changing the moment of inertia of the virus so that it cannot role synchronously on the wave that is created by the antigens (the targets of the virus). The virus is no longer able to detect the antigens.

We think that our model of phase locking of longitudinal electric THz fields can also be applied to the folding process of biomolecules such as proteins. The folding of molecules is an effective method to reduce the spring constant of molecular oscillators so that they can oscillate in the THz range. Each structural domain can be a local THz oscillator that makes a definite movement possible. This definite movement can be part of the folding process. Consequently applied, this model of phase locking, in combination with other known forces and chemical effects, would reduce the number of folding possibilities of a protein to one.

The long distance interaction between antibodies and antigens could be an explanation for the effect that in medicine is called immunogenicity.

Appendix 1: Energy supply

Energy supply for molecular oscillators

The basis of this theory is that the antigen has at least one oscillating structure and the antibody has two oscillating arms. But these structures can oscillate only if an energy supply comes from other components. We think energy is coming from parts (Brownian movement, mainly water molecules) in the liquid. If a part hits the mass of a molecular oscillator, the oscillator starts oscillating. The damped oscillator can be described by the equation of motion:

$$m\ddot{x} + d\dot{x} + cx = u(t) \tag{33}$$

with m: mass, d: damping constant, c: spring constant and $u(t)$: time-dependent function.

Laplace transformation of Eq. 33 gives the transfer function $G(s)$:

$$G(s) = \frac{X(s)}{U(s)} = L(m\ddot{x} + d\dot{x} + cx) = \frac{1}{m \cdot s^2 + d \cdot s + c} \tag{34}$$

The collision is a small energy pulse, which is in the ideal case a Dirac pulse $U(s) = 1$. Now $X(s)$ and $x(t)$ can be calculated.

$$X(s) = G(s) \cdot U(s)$$

$$X(s) = \frac{1}{ms^2 + d \cdot s + c} \cdot 1 = \frac{1/m}{s^2 + d/m \cdot s + c/m}$$

$$= X(s) = \frac{1}{m} \cdot \frac{1}{\sqrt{c \cdot m - d^2/4}} \cdot \frac{\sqrt{c \cdot m - d^2/4}}{\left(s + \frac{d/2}{m}\right)^2 + \left(\frac{c \cdot m - d^2/4}{m^2}\right)}$$

$$\Rightarrow x(t) = \frac{e^{\frac{-d}{2m}t}}{m\sqrt{c \cdot m - d^2/4}} \sin(\omega t)$$

with :

$$\omega = \sqrt{\frac{c \cdot m - d^2/4}{m^2}} \tag{35}$$

ω is the angular frequency of the oscillator.

After the collision the damped oscillator begins with oscillation. This means the antigen and the antibody arms will start oscillating automatically in a liquid with Brownian movement, if the condition $c \cdot m > d^2/4$ is fulfilled.

Appendix 2: Principle of linear momentum (motor and drive of the antibody)

According to our theory an antibody must have a motor. This motor drives the antibody so that it can reach the antigen in short time. We think the principle of linear momentum of an oscillator is used as motor and drive. The principle is demonstrated by reducing the heavy and the light chain of an antibody to two different masses (Fig. 5, m_3 and m_2).

A molecular oscillator is bound to a second mass so that the oscillator is defined by a mass-spring-mass system. One of the masses is bigger than the other. The bigger mass represents the heavy chain and the lighter mass the light chain of the antibody. In a liquid both masses (heavy and light chain of the antibody) are hit by the same number and size of parts from Brownian movement (the masses are hit mainly by water molecules). This brings energy to the

system. It can be mathematically proven that the energy transfer is independent of the amplitude of oscillation if the spring constant is linear. Then the energy transfer depends only on the match of masses. Figure 5 shows the case that m_1 hits the mass m_2 and m_4 hits the mass m_3 at the same moment.

The sum of energy and linear momentum before and after the hits must be the same.

For $\dot{x}_1^{'}$, $\dot{x}_2^{'}$, $\dot{x}_3^{'}$ and $\dot{x}_4^{'}$(speeds after collision) we get:

$$\begin{aligned}
&\frac{1}{2}m_1(\dot{x}_1)^2+\frac{1}{2}m_2(\dot{x}_2)^2=\frac{1}{2}m_1(\dot{x}_1^{'})^2+\frac{1}{2}m_2(\dot{x}_2^{'})^2\\
&m_1\cdot\dot{x}_1+m_2\cdot\dot{x}_2=m_1\cdot\dot{x}_1^{'}+m_2\cdot\dot{x}_2^{'}\\
&\Rightarrow\dot{x}_1^{'}=\frac{(m_1-m_2)\cdot\dot{x}_1+2m_2\cdot\dot{x}_2}{m_1+m_2}\\
&\Rightarrow\dot{x}_2^{'}=\frac{(m_2-m_1)\cdot\dot{x}_2+2m_1\cdot\dot{x}_1}{m_1+m_2}
\end{aligned}\tag{36}$$

$$\begin{aligned}
&\frac{1}{2}m_3(\dot{x}_3)^2+\frac{1}{2}m_4(\dot{x}_4)^2=\frac{1}{2}m_3(\dot{x}_3^{'})^2+\frac{1}{2}m_4(\dot{x}_4^{'})^2\\
&m_3\cdot\dot{x}_3+m_4\cdot\dot{x}_4=m_3\cdot\dot{x}_3^{'}+m_4\cdot\dot{x}_4^{'}\\
&\Rightarrow\dot{x}_3^{'}=\frac{(m_3-m_4)\cdot\dot{x}_3+2m_4\cdot\dot{x}_4}{m_3+m_4}\\
&\Rightarrow\dot{x}_4^{'}=\frac{(m_4-m_3)\cdot\dot{x}_4+2m_3\cdot\dot{x}_3}{m_3+m_4}
\end{aligned}\tag{37}$$

For the energy E_2 brought into the system over mass m_2 and energy E_3 brought into the system via mass m_3 we have:

$$\begin{aligned}
E_2&=\frac{1}{2}m_2\left((\dot{x}_2^{'})^2-(\dot{x}_2)^2\right)\\
E_2&=\frac{m_2}{2}\left(\left(\frac{(m_2-m_1)\cdot\dot{x}_2+2m_1\cdot\dot{x}_1}{m_1+m_2}\right)^2-(\dot{x}_2)^2\right)
\end{aligned}\tag{38}$$

$$\begin{aligned}
E_3&=\frac{1}{2}m_3\left((\dot{x}_3^{'})^2-(\dot{x}_3)^2\right)\\
E_3&=\frac{m_3}{2}\left(\left(\frac{(m_3-m_4)\cdot\dot{x}_3+2m_4\cdot\dot{x}_4}{m_3+m_4}\right)^2-(\dot{x}_3)^2\right)\\
E_3&=\frac{m_3}{2}\left(\frac{-4m_4m_3(\dot{x}_3)^2+4(m_4)^2(\dot{x}_4)^2+4m_4(m_3-m_4)\dot{x}_3\dot{x}_4}{(m_3+m_4)^2}\right)
\end{aligned}\tag{39}$$

A good mass match for maximal energy transfer is given for $m_1=m_2$, a bad mass match for minimal energy transfer for $m_2\gg m_1$. With $m=m_1=m_3=m_4$ and $\dot{x}_2=\dot{x}_3$ Eqs. 38 and 39 give:

$$\begin{aligned}
E_2&=\frac{m}{2}\left((\dot{x}_1)^2-(\dot{x}_2)^2\right)\\
E_2&=\frac{m}{2}(\dot{x}_1)^2-\frac{m}{2}(\dot{x}_2)^2\\
E_3&=\frac{m_3}{2}\left(\frac{-4m\cdot m_3(\dot{x}_3)^2+4m^2(\dot{x}_1)^2+4m(m_3-m)\dot{x}_3\dot{x}_1}{(m_3+m)^2}\right)\\
E_3&=\frac{m_3}{2}\left(\frac{-4m\cdot m_3(\dot{x}_3)^2+4m(m_3-m)\dot{x}_3\dot{x}_1}{(m_3+m)^2}\right)\\
&\quad+\frac{m_3}{2}\frac{4m^2(\dot{x}_1)^2}{(m_3+m)^2}
\end{aligned}\tag{40}$$

The masses m_3 and m_4 are oscillating. This oscillation can be described by:

$$\begin{aligned}
\dot{x}_2&=A_2\sin\alpha_2\\
\dot{x}_3&=A_3\sin\alpha_3
\end{aligned}\tag{41}$$

if the spring constant is linear.

After inserting Eq. 41 in Eq. 40 differentiation gives:

$$\begin{aligned}
&\frac{\partial E_2}{\partial\alpha_2}=-m(A_2)^2\sin\alpha_2\cos\alpha_2\\
&\frac{\partial E_3}{\partial\alpha_3}=\frac{m_3}{2}\\
&\left(\frac{-8(A_3)^2m\cdot m_3\sin\alpha_3\cos\alpha_3+4A_3m(m_3-m)\dot{x}_1\cos\alpha_3}{(m_3+m)^2}\right)
\end{aligned}\tag{42}$$

Now it follows from Eqs. 40, 41 and 42 after one oscillation period:

$$\begin{aligned}
E_2&=\frac{m}{2}(\dot{x}_1)^2-\int_0^{2\pi}(m(A_2)^2\sin\alpha_2\cos\alpha_2)d\alpha_2\\
E_2&=\frac{m}{2}(\dot{x}_1)^2
\end{aligned}\tag{43}$$

$$\begin{aligned}
E_3&=\frac{m_3}{2}\cdot\frac{2m^2(\dot{x}_1)^2}{(m_3+m)^2}+\int_0^{2\pi}\frac{m_3}{2}\\
&\left(\frac{-8(A_3)^2m\cdot m_3\sin\alpha_3\cos\alpha_3+4A_3m(m_3-m)\dot{x}_1\cos\alpha_3}{(m_3+m)^2}\right)d\alpha_3\\
E_3&=\frac{m_3}{2}\cdot\frac{2m^2(\dot{x}_1)^2}{(m_3+m)^2}
\end{aligned}\tag{44}$$

The energy difference $\Delta E=E_2-E_3$ is responsible for a movement of the mass-spring-mass system.

We get for ΔE:

$$\Delta E = \left(\frac{m}{2} - \frac{m_3}{2}\left(\frac{2m^2}{(m_3+m)^2}\right)\right) \cdot (\dot{x}_1)^2 \tag{45}$$

For $m_3 > m$ we always get $\Delta E > 0$.

Appendix 3: Oscillation control of principle of linear momentum (steering of an antibody)

If a biological macromolecule like an antibody uses the principle of linear momentum for driving the molecule, it makes sense that the principle of linear momentum can be controlled by another quantity. The amplitude of oscillation can be such a quantity. Figure 5 shows two masses that are connected by a spring; one of these masses represents the heavy chain of the antibody (m_3) and the other mass represents the light chain of the antibody (m_2). If the mass-spring-mass system has a linear spring characteristic, it is not possible to control the forward movement by the amplitude of oscillation. This changes if the spring shows nonlinear (progressive) behavior likes a rubber band (see spring characteristic, Fig. 5). We think molecular bindings often have a progressive spring characteristic like a rubber band. This type of progressive spring characteristic has already been found for biological macromolecules (Schoenauer et al. 2005). The spring constant varies in the described example between 2×10^{-4} N/m and 8.6×10^{-3} N/m.

For the two extreme positions (minimal and maximal position of x_2 and x_3) the masses $m_1 = m$ and $m_4 = m$ both see the mass combination $m_2 + m_3 = m + m_3$. We now have for the extreme positions no driving power ($\Delta E = 0$). For the position where the spring is not spanned the driving power still exists. The systematic movement depends now on the amplitude of oscillation. Minimal oscillation amplitude gives maximal movement; maximal oscillation amplitude gives minimal movement. The movement always goes in the direction of the bigger mass (heavy chain). This shows that an antibody can be steered simply by controlling the oscillation amplitude of both antibody arms.

Appendix 4: Calculation of the differential quotients $\frac{\partial F_0(x_1)}{\partial x_2}$ and $\frac{\partial F_0(x_2)}{\partial x_1}$

For the interaction force F_0 between the two oscillating masses of the antibody we get:

$$F_0 = -F_0(G) + F_0(E) = \frac{-G_{\text{corr}}m^2 + k_{\text{corr}}q^2}{D^2}$$

with:

$$D_{\text{Phys}} = \sqrt{(2l - x_1 - x_2)^2 \cdot \sin^2\alpha + (x_1 - x_2)^2 \cdot \cos^2\alpha}$$

$$D = n_{\text{THz}} \cdot D_{\text{Phys}}$$

$$\kappa_{\text{Re}} = (\text{Re}(\varepsilon_{\text{THz}}) \cdot \text{Re}(\mu_{\text{THz}}) - \text{Im}(\varepsilon_{\text{THz}}) \cdot \text{Im}(\mu_{\text{THz}})$$

$$\kappa_{\text{Im}} = (\text{Re}(\varepsilon_{\text{THz}}) \cdot \text{Im}(\mu_{\text{THz}}) + \text{Im}(\varepsilon_{\text{THz}}) \cdot \text{Re}(\mu_{\text{THz}})$$

$$n_{\text{THz}} = \sqrt{\frac{1}{2}\sqrt{(\kappa_{\text{Re}})^2 + (\kappa_{\text{Im}})^2} + \kappa_{\text{Re}}}$$

$$k_{\text{THz}} = \sqrt{\frac{1}{2}\sqrt{(\kappa_{\text{Re}})^2 + (\kappa_{\text{Im}})^2} - \kappa_{\text{Re}}}$$

$$G_{\text{corr}} = G \cdot n_{\text{THz}}$$

$$G = 6.67428 \cdot 10^{-11}\,\frac{\text{Nm}^2}{\text{kg}^2}$$

$$k_{\text{corr}} = k_e \cdot e^{-k_{\text{THz}}}$$

$$k_e = 8.98755178 \cdot 10^9\,\frac{\text{Nm}^2}{C} \tag{46}$$

ε_{THz}: Relative permittivity of ambient medium (complex value), μ_{THz}: relative permeability of the ambient medium, κ_{Re}: real part of effective permittivity of ambient medium, κ_{Im}: imaginary part of effective permittivity of ambient medium, n_{THz}: real part of refractive index of the ambient medium, k_{THz}: imaginary part of the refractive index of the ambient medium, D_{Phys}: physical distance, D: optical distance.

The gravitation force component $F_0(G)$ and the coulomb force component $F_0(E)$ have different directions.

After splitting the force F_0 into components in x_1 and x_2 direction $F_0(x_1)$, and $F_0(x_2)$ we have:

$$F_0(x_1) = -F_0 \sin(\alpha - \theta)$$

$$F_0(x_2) = -F_0 \sin(\alpha + \theta)$$

with:

$$\theta = \arctan\left(\frac{(x_1 - x_2)}{(2l - x_1 - x_2)\tan\alpha}\right) \tag{47}$$

For small movements $x_1 << l, x_2 << l, \theta \approx 0$ we can find:

$$F_0 = \frac{-G_{\text{corr}}m^2 + k_{\text{corr}}q^2}{(n_{\text{THz}})^2(2l - x_1 - x_2)^2 \sin^2\alpha + (x_1 - x_2)^2 \cos^2\alpha} \tag{48}$$

$$\theta \approx \frac{x_1 - x_2}{2l \cdot \tan\alpha} \tag{49}$$

Then we get from Eq. 47 for the coupling of the arm oscillators:

$$
\begin{aligned}
F_0(x_1) &= -F_0 \sin(\alpha - \theta) \\
F_0(x_1) &= -F_0(\sin\alpha \cdot \cos\theta - \cos\alpha \cdot \sin\theta) \\
F_0(x_1) &\approx -F_0 \sin\alpha + F_0 \cos\alpha \frac{x_1 - x_2}{2l \cdot \tan\alpha} \\
\frac{\partial F_0(x_1)}{\partial x_2} &\approx -2 \cdot (n_{\mathrm{THz}})^2 \sin\alpha \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2) \cdot \left((x_1 - x_2)\cos^2\alpha + (2l - x_1 - x_2)\sin^2\alpha\right)}{D^4} \\
&\quad + (n_{\mathrm{THz}})^2 \cos\alpha \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2) \cdot \left((x_1 - x_2)\cos^2\alpha + (2l - x_1 - x_2)\sin^2\alpha\right)}{l \cdot \tan\alpha \cdot D^4} \\
&\quad - \cos\alpha \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2)}{2l \cdot \tan\alpha \cdot D^2} \\
\frac{\partial F_0(x_1)}{\partial x_2} &\approx -2 \cdot (n_{\mathrm{THz}})^2 \cdot \sin^3\alpha \cdot (2l - x_1 - x_2) \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2)}{D^4} - \cos\alpha \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2)}{2l \cdot \tan\alpha \cdot D^2}
\end{aligned}
\tag{50}
$$

$$
\begin{aligned}
F_0(x_2) &= -F_0 \sin(\alpha + \theta) \\
F_0(x_2) &= -F_0(\sin\alpha \cdot \cos\theta + \cos\alpha \cdot \sin\theta) \\
F_0(x_2) &\approx -F_0 \sin\alpha - F_0 \cos\alpha \frac{x_1 - x_2}{2l \cdot \tan\alpha} \\
\frac{\partial F_0(x_2)}{\partial x_1} &\approx -2 \cdot (n_{\mathrm{THz}})^2 \sin\alpha \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2) \cdot \left(-(x_1 - x_2)\cos^2\alpha + (2l - x_1 - x_2)\sin^2\alpha\right)}{D^4} \\
&\quad + (n_{\mathrm{THz}})^2 \cos\alpha \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2) \cdot \left(-(x_1 - x_2)\cos^2\alpha + (2l - x_1 - x_2)\sin^2\alpha\right)}{l \cdot \tan\alpha \cdot D^4} \\
&\quad - \cos\alpha \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2)}{2l \cdot \tan\alpha \cdot D^2} \\
\frac{\partial F_0(x_2)}{\partial x_1} &\approx -2 \cdot (n_{\mathrm{THz}})^2 \sin^3\alpha (2l - x_1 - x_2) \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2)}{D^4} - \cos\alpha \frac{(-G_{\mathrm{Corr}} m^2 + k_{\mathrm{corr}} q^2)}{2l \cdot \tan\alpha \cdot D^2}
\end{aligned}
\tag{51}
$$

It follows: $\frac{\partial F_0(x_1)}{\partial x_2} \approx \frac{\partial F_0(x_2)}{\partial x_1}$.

Appendix 5: Calculation of the differential quotients $\frac{\partial F_1(x_1)}{\partial x_1}$ and $\frac{\partial F_2(x_2)}{\partial x_2}$

If the optical distance d to the antigen is long in relation to D it can be simplified:

$$
\begin{aligned}
&\gamma \approx 0^\circ \\
&\delta \approx 0^\circ \\
&d_1 = n_{\mathrm{THz}} \cdot z_1 \approx d_2 = n_{\mathrm{THz}} \cdot z_2 \approx d = n_{\mathrm{THz}} \cdot z \\
&\frac{|F_1|}{F_1} = \frac{|F_2|}{F_2}
\end{aligned}
\tag{52}
$$

n_{THz}: Real part of refractive index of the ambient medium.

Then we get for F_1 and F_2:

$$
F_1 \approx \frac{-G_{\mathrm{corr}} M \cdot m + k_{\mathrm{corr}} Q \cdot q}{(d + x_1 \cdot n_{\mathrm{THz}} \cdot \cos\alpha)^2} \tag{53}
$$

$$
F_2 \approx \frac{-G_{\mathrm{corr}} M \cdot m + k_{\mathrm{corr}} Q \cdot q}{(d + x_2 \cdot n_{\mathrm{THz}} \cdot \cos\alpha)^2} \tag{54}
$$

For the force component in x_1 and x_2 direction it follows:

$$
\begin{aligned}
F_1(x_1) &= F_1(\cos\alpha \cdot \cos\gamma - \sin\alpha \cdot \sin\gamma) \\
&\approx \frac{-G_{\mathrm{corr}} M \cdot m + k_{\mathrm{corr}} Q \cdot q}{(d + x_1 \cdot n_{\mathrm{THz}} \cdot \cos\alpha)^2} \cos(\alpha + \gamma)
\end{aligned}
\tag{55}
$$

$$
\begin{aligned}
F_2(x_2) &= F_2(\cos\alpha \cdot \cos\gamma + \sin\alpha \cdot \sin\gamma) \\
&\approx \frac{-G_{\mathrm{corr}} M \cdot m + k_{\mathrm{corr}} \cdot Q \cdot q}{(d + x_2 \cdot n_{\mathrm{THz}} \cdot \cos\alpha)^2} \cos(\alpha - \gamma)
\end{aligned}
\tag{56}
$$

After differentiation we get from Eq. 55 and Eq. 56:

$$
\begin{aligned}
&\frac{\partial F_1(x_1)}{\partial x_1} \\
&\approx \frac{-2 n_{\mathrm{THz}} (-G_{\mathrm{corr}} M \cdot m + k_{\mathrm{corr}} Q \cdot q) \cos\alpha \cdot \cos(\alpha + \gamma)}{(d + x_1 \cdot n_{\mathrm{THz}} \cdot \cos\alpha)^3} \\
&\frac{\partial F_1(x_1)}{\partial x_1} \\
&\approx \frac{-2 n_{\mathrm{THz}} (-G_{\mathrm{corr}} M \cdot m + k_{\mathrm{corr}} Q \cdot q) \cos\alpha \cdot \cos(\alpha + \gamma)}{d^3}
\end{aligned}
\tag{57}
$$

$$\frac{\partial F_2(x_2)}{\partial x_2} \approx \frac{-2n_{\mathrm{THz}}(-G_{\mathrm{corr}}M\cdot m + k_{\mathrm{corr}}Q\cdot q)\cos\alpha\cdot\cos(\alpha-\gamma)}{(d+x_2\cdot n_{\mathrm{THz}}\cdot\cos\alpha)^3} \quad (58)$$

$$\frac{\partial F_2(x_2)}{\partial x_2} \approx \frac{-2n_{\mathrm{THz}}(-G_{\mathrm{corr}}M\cdot m + k_{\mathrm{corr}}Q\cdot q)\cos\alpha\cos(\alpha-\gamma)}{d^3}$$

Appendix 6: Calculation of the eigenvalue equation

The equation of motion received from Fig. 6 gives:

$$m\ddot{x}_1 + c_1(x_1-y_1) + c_2y + \frac{\partial F_0(x_1)}{\partial x_2}x_2 + \frac{\partial F_1(x_1)}{\partial x_1}x_1 = 0$$

$$m\ddot{x}_2 + c_1(x_2-y_2) + c_2y + \frac{\partial F_0(x_2)}{\partial x_1}x_1 + \frac{\partial F_2(x_2)}{\partial x_2}x_2 = 0$$

with:

$$y = y_1\cos\alpha = y_2\cos\alpha$$

$$x_1c_1\cos\alpha + x_2c_1\cos\alpha = yc_2$$

$$y = \frac{c_1\cos\alpha}{c_2}(x_1+x_2) \quad (59)$$

From (59) we get:

$$m\ddot{x}_1 + c_1\left(x_1 - \frac{c_1}{c_2}(x_1+x_2)\right) + c_1\cos\alpha(x_1+x_2) + \frac{\partial F_0(x_1)}{\partial x_2}x_2 + \frac{\partial F_1(x_1)}{\partial x_1}x_1 = 0$$

$$m\ddot{x}_1 + \left[c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right) + \frac{\partial F_1}{\partial x_1}\right]x_1 - \left[c_1\left(\frac{c_1}{c_2}-\cos\alpha\right) - \frac{\partial F_0(x_1)}{\partial x_2}\right]x_2 = 0$$

$$m\ddot{x}_2 + c_1\left(x_2 - \frac{c_1}{c_2}(x_1+x_2)\right) + c_1\cos\alpha(x_1+x_2) + \frac{\partial F_0(x_2)}{\partial x_1}x_1 + \frac{\partial F_2(x_2)}{\partial x_2}x_2 = 0$$

$$m\ddot{x}_2 + \left[c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right) + \frac{\partial F_2}{\partial x_2}\right]x_2 - \left[c_1\left(\frac{c_1}{c_2}-\cos\alpha\right) - \frac{\partial F_0(x_2)}{\partial x_1}\right]x_1 = 0 \quad (60)$$

Important is that $\frac{\partial F_0(x_1)}{\partial x_2}$ and $\frac{\partial F_0(x_2)}{\partial x_1}$ are negative because $k_{\mathrm{corr}}q^2 \gg G_{\mathrm{corr}}m^2$. So the strong electrical coupling of the antibody arms is compensated by spring c_2. This makes phase locking to external electromagnetic fields possible.

With the mathematical substitutions $x_1 = A_1e^{\lambda t}$ and $x_2 = A_2e^{\lambda t}$ we get from Eq. 60:

$$m\lambda^2A_1e^{\lambda t} + \left[c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right) + \frac{\partial F_1(x_1)}{\partial x_1}\right]A_1e^{\lambda t} - \left[c_1\left(\frac{c_1}{c_2}-\cos\alpha\right) - \frac{\partial F_0(x_1)}{\partial x_2}\right]A_2e^{\lambda t} = 0$$

$$m\lambda^2A_2e^{\lambda t} + \left[c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right) + \frac{\partial F_2(x_2)}{\partial x_2}\right]A_2e^{\lambda t} - \left[c_1\left(\frac{c_1}{c_2}-\cos\alpha\right) - \frac{\partial F_0(x_2)}{\partial x_1}\right]A_1e^{\lambda t} = 0 \quad (61)$$

This is a linear equation system with two unknown quantities A_1 and A_2. Equation 61 can be written in the matrix form:

$$\bar{T}\cdot\vec{A} = \vec{0} = \begin{bmatrix} m\lambda^2 + \left[c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right) + \frac{\partial F_1(x_1)}{\partial x_1}\right] & -\left[c_1\left(\frac{c_1}{c_2}-\cos\alpha\right) - \frac{\partial F_0(x_1)}{\partial x_2}\right] \\ -\left[c_1\left(\frac{c_1}{c_2}-\cos\alpha\right) - \frac{\partial F_0(x_2)}{\partial x_1}\right] & m\lambda^2 + \left[c_1\left(1+\cos\alpha-\frac{c_2}{c_2}\right) + \frac{\partial F_2(x_2)}{\partial x_2}\right] \end{bmatrix}\cdot\begin{bmatrix}A_1\\A_2\end{bmatrix} = \begin{bmatrix}0\\0\end{bmatrix} \quad (62)$$

For getting non-trivial solutions for λ the determinate of $\bar{T}$must be 0:

$$\det(\bar{T}) = \left(m\lambda^2 + \left[c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right) + \frac{\partial F_1(x_1)}{\partial x_1}\right]\right)\cdot\left(m\lambda^2 + \left[c_1\left(1+\cos\alpha-\frac{c_1}{c_2}\right) + \frac{\partial F_2(x_2)}{\partial x_2}\right]\right) - \left(c_1\left(\frac{c_1}{c_2}-\cos\alpha\right) - \frac{\partial F_0(x_2)}{\partial x_1}\right)\cdot\left(c_1\left(\frac{c_1}{c_2}-\cos\alpha\right) - \frac{\partial F_0(x_1)}{\partial x_2}\right) = 0 \quad (63)$$

Appendix 7: Calculation of the $A_1 = f(A_2)$ relationship

The relevant relationship can be calculated from the matrix form of the equation of motion.

With $(\lambda_1)^2 = -(\omega_1)^2$ we get from (15) (18), and (62):

$$\begin{bmatrix} -\frac{-k_1+k_2-\sqrt{k_1^2-2k_1k_2+k_2^2+4k_3^2}}{2} & -k_3 \\ -k_3 & -\frac{-k_2+k_1-\sqrt{k_1^2-2k_1k_2+k_2^2+4k_3^2}}{2} \end{bmatrix} \cdot \begin{bmatrix} A_1 \\ A_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$$

$$\rightarrow A_1 = -\frac{2k_3}{-k_1+k_2-\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}} A_2$$

and

$$\rightarrow A_1 = -\frac{-k_2+k_1-\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2k_3} A_2 \tag{64}$$

With $(\lambda_2)^2 = -(\omega_2)^2$ we get from (15) (18), and (62):

$$\begin{bmatrix} -\frac{-k_1+k_2+\sqrt{k_1^2-2k_1k_2+k_2^2+4k_3^2}}{2} & -k_3 \\ -k_3 & -\frac{-k_2+k_1+\sqrt{k_1^2-2k_1k_2+k_2^2+4k_3^2}}{2} \end{bmatrix} \cdot \begin{bmatrix} A_1 \\ A_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$$

$$\rightarrow A_1 = -\frac{2k_3}{-k_1+k_2+\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}} A_2$$

and

$$\rightarrow A_1 = -\frac{-k_2+k_1+\sqrt{(k_1)^2-2k_1k_2+(k_2)^2+4(k_3)^2}}{2k_3} A_2 \tag{65}$$

Appendix 8: Calculation of coupled arm oscillations

The now following complete calculation is done for the case that the antigen is straight ahead of the antibody. For this case we get as possible solutions:

$$\begin{aligned} &x_1 = x_2 = A_1 \cdot e^{i\omega_1 t}, x_1 = x_2 = A_1 \cdot e^{-i\omega_1 t} \\ &x_1 = -x_2 = A_1 \cdot e^{i\omega_2 t}, x_1 = -x_2 = A_1 \cdot e^{-i\omega_2 t} \end{aligned} \tag{66}$$

The result of the differential equation is a combination of linear independent homogeneous results. We get:

$$\begin{aligned} &x_1 = C_1 \cdot e^{i\omega_1 t} + C_2 \cdot e^{-i\omega_1 t} + C_3 \cdot e^{i\omega_{2a}} + C_4 \cdot e^{-i\omega_2 t} \\ &x_2 = C_1 \cdot e^{i\omega_1 t} + C_2 \cdot e^{-i\omega_1 t} - C_3 \cdot e^{i\omega_2 t} - C_4 \cdot e^{-i\omega_2 t} \\ &C_i \in C \end{aligned} \tag{67}$$

By use of $e^{i\omega t} = \cos\omega t + j\sin\omega t, e^{-i\omega t} = \cos\omega t - j\sin\omega t$ we can transform (67) to

$$\begin{aligned} x_1 &= B_1 \cdot \cos(\omega_1 t + \phi_1) + B_2 \cdot \cos(\omega_2 t + \phi_2) \\ x_2 &= B_1 \cdot \cos(\omega_1 t + \phi_1) - B_2 \cdot \cos(\omega_2 t + \phi_2) \end{aligned} \tag{68}$$

To prove this we bring the results into one form by the following substitutions:

$$\begin{aligned} \xi^+ &= x_1 + x_2 \\ \xi^- &= x_1 - x_2 \end{aligned} \tag{69}$$

With:

$$\begin{aligned} k_1 &= c_1\left(1 + \cos\alpha - \frac{c_1}{c_2}\right) + \frac{\partial F_1(x_1)}{\partial x_1} = k_2 \\ k_2 &= c_1\left(1 + \cos\alpha - \frac{c_1}{c_2}\right) + \frac{\partial F_2(x_2)}{\partial x_2} \\ k_3 &= c_1\left(\frac{c_1}{c_2} - \cos\alpha\right) - \frac{\partial F_0(x_2)}{\partial x_1} \end{aligned} \tag{70}$$

we obtain in our new system:

$$\begin{aligned} m\ddot{\xi}^+ &= m\frac{\partial^2\xi^+}{\partial t^2} = m\ddot{x}_1 + m\ddot{x}_2 \\ m\ddot{\xi}^+ &= -(k_1 - k_3)(x_1 + x_2) = -(k_1 - k_3)\xi^+ \\ m\ddot{\xi}^+ &= -2B_1(k_1 - k_3)\cos(\omega_1 t + \phi_1) \\ m\ddot{\xi}^- &= m\frac{\partial^2\xi^-}{\partial t^2} = m\ddot{x}_1 - m\ddot{x}_2 \\ m\ddot{\xi}^- &= -(k_1 + k_3)(x_1 - x_2) = -(k_1 + k_3)\xi^- \\ m\ddot{\xi}^- &= -2B_2(k_1 + k_3)\cos(\omega_2 t + \phi_2) \end{aligned} \tag{71}$$

It follows:

$$\begin{aligned} \xi^+ &= \iint\left(\frac{-2B_1(k_1 - k_3)}{m}\cos(\omega_1 t + \phi_1)\right)\mathrm{d}t\mathrm{d}t \\ &= A_1\cos(\omega_1 t + \phi_1) \\ \xi^- &= \iint\left(\frac{-2B_2(k_1 + k_3)}{m}\cos(\omega_2 t + \phi_2)\right)\mathrm{d}t\mathrm{d}t \\ &= A_2\cos(\omega_2 t + \phi_2) \end{aligned}$$

with:

$$\begin{aligned} A_1 &= \frac{2B_1(k_1 - k_3)}{m(\omega_1)^2} = 2B_1 \\ A_2 &= \frac{2B_1(k_1 + k_3)}{m(\omega_2)^2} = 2B_2 \\ \omega_1 &= \sqrt{\frac{k_1 - k_3}{m}} \\ \omega_2 &= \sqrt{\frac{k_1 + k_3}{m}} \\ A_1, A_2, \phi_2 &\in R \end{aligned} \tag{72}$$

Then we get with $A = A_1 = A_2$:

$$
\begin{aligned}
x_1 &= \frac{\xi^+ + \xi^-}{2} = \frac{A}{2}(\cos(\omega_1 t + \phi_1) + \cos(\omega_2 t + \phi_2)) \\
x_1 &= \frac{A}{2}\cos\left(\frac{(\omega_1 + \omega_2)t + \phi_1 + \phi_2}{2}\right) \\
&\quad \cos\left(\frac{(\omega_1 - \omega_2)t + (\phi_{_1} - \phi_2)}{2}\right) \\
x_2 &= \frac{\xi^+ - \xi^-}{2} = \frac{A}{2}(\cos(\omega_1 t + \phi_1) - \cos(\omega_2 t + \phi_2)) \\
x_2 &= -\frac{A}{2}\sin\left(\frac{(\omega_1 + \omega_2)t + \phi_1 + \phi_2}{2}\right) \\
&\quad \sin\left(\frac{(\omega_1 - \omega_2)t + (\phi_1 - \phi_2)}{2}\right)
\end{aligned}
\tag{73}
$$

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