action potential transfer occurred with no measurable delay. However, in a partially uncoupled cell pair displaying an r_n of the order of 1000 MΩ, there was no action potential transfer detectable.

Conclusions

The experiments described in this paper have been carried out on cell pairs isolated from adult rat and guinea pig ventricles by means of an enzymatic procedure. Electrical measurements indicated that the pairs of myocytes remained coupled electrically. They represent a convenient cellular preparation for investigating the electrical and pharmacological properties of the nexal membrane. Furthermore, cell pairs provide a useful model to explore the characteristics of action potential transfer at the single nexus level.

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Full Papers

Metabolic iteration, evolution and cognition in cellular proliferation

E. Cervén

Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo 113 (Japan), 5 February 1987

Summary. A model for cellular proliferation is described according to which proliferation ensues when metabolism evolves towards commitment to DNA synthesis, and inhibition of proliferation occurs when enzymic interactions are iterated within a few metabolic pathways, another limiting factor being the supply of metabolites. The model successfully describes cellular growth and division as a 'cognitive process' based on interaction within enzymic elements and the genome, and affords an explanation in these terms of some empirical phenomena which have previously been understood only as isolated observations.
Key words. Cognitive processes; metabolism; evolution; biomathematical models; cell proliferation; cell growth.

Introduction

No simple model to explain the observed relationships between cell volume, cell mass, protein synthesis, metabolism, cellular morphology, and cell proliferation has so far been presented, although correlations between these entities have been amply investigated. For example, a correlation exists between the frequency of cell division and growth of cell mass, cell volume and cell surface area per unit time[1–6]. This correlation tends to be straightforwardly linear, i.e. the cells maintain their size under permissive nutritive conditions, while under excessive or deficient nutritive conditions[7,8] or during morula formation in embryogenesis, the timing of the determination of size may lag one or more cell generations. Both commitment to DNA synthesis[9,10] and subsequent metabolic evolution[7] tend to be probabilistic events. There is also a correlation between cell division and various metabolic rates, such as transport of metabolites[11–17], Ca^{2+}-entry into the cell[9,18], Na^+-entry[19], Na^+K^+-pump activity[19–21], Na^+H^+-exchange with cytoplasmic alkalinization[22–24] and phosphoinositide turnover[25–27]. Other mitogenic events which do not themselves belong to the category of changes of flux include e.g. binding to the cell surface of growth factors[22,28–30] or other specific ligands[20,21] and protein kinase C-activa-

tion[28,32,33], and are mostly effective via the plasma membrane[34,35]. Furthermore, a lack of distinct morphology of cells the metabolism of which is directed towards division has been noticed[36–40], something which is also related to the lack of topoinhibition of growth and movement of tumorous cells[9,41,42], and is one of the fundamental unsolved questions in cancer research[43,44]. Suppression of growth of animal cells is observed when the internalized quantity of the required metabolites has been insufficient to reach the threshold for commitment to DNA synthesis[7–10,45–47]. This is the case, either when the medium contains a sub-optimal amount of metabolites[46,47] or when the transport of metabolites is suppressed, for example by limited diffusion[9,48] or in the presence of mitotic inhibitors[49–54]. The latter is typical of cells resting in the nutritious internal environment of an organism, where morphological disassembly, enhancement of metabolite transport and cell division can be initiated even by a slight specific[20,22,28–31] (or unspecific) perturbation of the cellular envelope[34,35]. A reversal of this is the reversed transformation of tumor cells obtained by covering their surface with macromolecules[55–57] or by increasing the intracellular level of cyclic AMP[58–61]. Following such treatment, there is a morphological assembly sometimes accompanied by differentiation, inhibition of transport of certain metabolites, and a delay or interruption of cellular division.

The above is interpretable in terms of fluxes of metabolites, which mediate probabilistic interactions between enzymic volume elements leading to metabolic evolution within the framework supplied by the genome. In stationary cells, the same enzymic and morphological contexts are stabilized by iteration, while in proliferating cells the metabolic 'attention' is focussed along an evolving string of genomic elements, leading to destabilization of transient structures or enzymic 'concepts'. This is adequately described by the formalism of 'cognitive processes'[62,63]. The model presented is compatible with the idea of self replication (iteration, stability) and evolution (diversity) as being the essential principles of life[64–66] and reduces the concept of metabolic control to a notion equivalent to 'inhibition of metabolic evolution' or 'desuppression of metabolic iteration'.

Sets of enzymes

In order to describe cellular growth and division, the formalism of 'cognitive processes'[62,63] is chosen. Metabolism is represented by a process involving dynamically interacting cognitive elements, the enzymes. Two sets of partly overlapping enzymic elements, Q_X and Q_D, are defined; these are the operative enzymes working in time intervals t_X and t_D in the G_0 (G_1) phases, and the enzymes effective from commitment to DNA synthesis until completion of division, respectively. Each element is composed of a number of sub-elements Q_i, which represent the species of enzymes, interacting via their sub-elements, the metabolites, reducing equivalents and electrons. An enzyme is then considered in its widest sense, i.e. as an element of a biological cell which can carry and transfer moving sub-elements.

After commitment to DNA synthesis, the enzymes belonging to Q_D are automatically switched on[7–10]. These carry out identical functions irrespective of the stage of differentiation, while the operative enzymes identify the stage of differentiation. In subsequent cell generations, different properties are often expressed such that the cell line evolves according to the partly overlapping scheme $Q_A \rightarrow Q_D \rightarrow Q_B \rightarrow Q_D \rightarrow Q_C \rightarrow \ldots$

There is a positive correlation between the frequency of cell division and the rate of anabolic metabolism as reflected by the increase in cell mass, cell volume, and cell surface area[1–6], observed under permissive nutritive conditions. The timing of the molecular events regulating the proportionality is

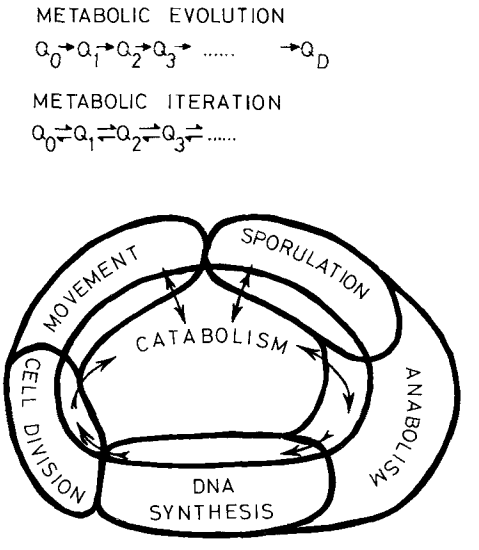

Figure 1. Illustration of metabolic evolution and iteration. Sets of enzymes expressed during a time interval, t, are represented by the letter Q, where the indices represent that at least one different enzyme is included or excluded relative to other time intervals. Either metabolism evolves towards DNA synthesis or focusses in a limited number of enzymic pathways (iteration). The main categories of metabolism essential for the survival of the cell, catabolism, movement, sporulation, anabolism, DNA synthesis and cell division, are indicated in the lower half of the figure, and the circulation or iteration of the main focus of enzymic interactions illustrated by arrows.

complex[7,8] but the final outcome is that proliferating cells that are dependent on exogenous supply of metabolites grow to a size which is of the same order of magnitude as that of the cell from which they originated, which in the majority of cases implicates a linear relationship. This can be interpreted as being due to the successive desuppression of more operons by the various metabolites and end products arising in a well nourished cell. The metabolic evolution can be described by the scheme $Q_1 \rightarrow Q_2 \rightarrow Q_3 \rightarrow Q_4 \cdots Q_D$, i.e. the activity is focussed at one point at a time, the transition from one set of enzymes to another partly overlapping one being a probability function of the metabolites and other desuppressive factors present in the cell. In contrast to this, if suppressors operate at any point of transition between different sets of enzymes, or if the incoming metabolites are otherwise taken care of by a restricted number of pathways, the metabolic evolution will be replaced by iteration, concentrating on a few metabolic points, as described by the scheme $Q_1 \rightleftharpoons Q_2 \rightleftharpoons Q_3 \rightleftharpoons \ldots$ As a consequence of the continuous input of metabolites and environmental changes, the emphasis on these points will be weighted in favor of the set of enzymes which most adequately responds to the actual environment (fig. 1). The successive activation of operons and metabolic pathways is rather similar, at least superficially, to the successive population of higher energy levels of electron shells in an atom. In the former case, more and more metabolic diversity and, in most cases, energy, is required to realize the basic elements of metabolism, while the pathways of cellular replication are ultimately activated.

Probabilities of interaction

For any rate of metabolism, there are two ways in which the probabilities of interaction between two enzymes, k and l, can increase. These are either an increase in the number of copies of the receiving enzyme, l, or a decrease of the distance between the two interacting enzymes. The first of these mech-

anisms is the 'induction' of new copies of enzyme using DNA and RNA as templates. If an enzyme, k, can interact with C_k other equally accessible enzymes and one of these, l, is variable in amount as a result of induction and breakdown, the probability of interaction from k to l, p_{kl}, is proportional to the number of copies of l present. If the number of copies of l is k_l, the probability is given by $p = k_l/C_k$ and this increases for each additional copy of l which is synthesized so that:

$$p_{kl} = \frac{k_l + X}{C_k + X} \quad (1)$$

where X is unity if a copy of the enzyme l has been synthesized as a result of induction and zero otherwise.

The probability of interaction also increases if the enzymes are brought closer as a result of previous interactions. This is common in living cells, e.g. when glycolytic enzymes become insoluble as a result of glycolytic activity, leading to a decreased pH[67], or when myosin becomes regularly spaced and organized during contraction[68,69]. Electron microscopic evidence indicates that most cellular proteins and enzymes are insoluble in cytoplasmic trabeculae which are broken down when metabolism stops after cytolysis[70]. The mechanisms by which such structures, which are called direct transfer pathways[71] could be held together on the cellular level has previously been discussed in terms of *long range forces requiring metabolism*[72]. The proximity of two interacting enzymes means that other enzymes are shielded from the possibility of interaction, which can be described by replacing the number C_k with a smaller number c_k such that $k_l \leq c_k < C_k$.

In addition to these factors increasing the probability of interaction, there are mechanisms which strive in the opposite direction. These are physical, such as diffusion, or chemical, such as proteolytic breakdown or end-product inhibition, and are especially evident in the Brownian motion observed when metabolism stops[73]. Many of these processes are time-dependent exponential decays, either of the simplest kind, or with slight variations.

Considering the above, it is reasonable to describe the process of metabolic interaction from one enzyme k to another enzyme l by the probability of interaction, p_{kl+}:

$$p_{kl+} = \frac{k_l + X}{c_k + X} \, e^{-A_{kl}\tau} \quad (2)$$

where X is unity if a new molecule of enzyme, l, is synthesized for example as a result of induction when a metabolite has escaped the enzyme k to interact with the genome. k_l is the number of copies of the enzyme l, and c_k the number of all enzymes with which the enzyme k can interact, taking into account the effective steric exclusion of other enzymes. c_k equals k_l when the two enzymes are held together in a tight structure, and is a higher number than k_l when the enzymes are randomized. The use of c_k in the interval $k_l \leqslant c_k < C_k$ occurs when the enzymes are compartmentalized, a common empirical observation. τ is the time between a previous metabolic interaction and the actual moment when the enzyme k binds a metabolite to account for the interaction described by the equation. A is a parameter relating to the stability against breakdown of the enzyme l and of the enzymic structure of which it forms a part. It is an inverse function of the amount of previous interactions within the same enzymic context, and is called the 'association parameter'[63]. Inasmuch as c_k decreases when A decreases, eq. (2) accounts for stabilization of an enzymic concept that is iterated. An exact empirical investigation is presently out of reach, but it suffices to note that with the given prerequisites, eq. (2) can be elaborated to describe stabilization of the probability of interaction between two enzymic elements as a consequence of iteration. Since the enzymes have volume, the metabolic stabilization also means stabilization of volume elements, i.e. increased order. Evidence of metabolic structures has previously been reported as the 'phenomenological topography' of enzymes in the plasma membrane of Ehrlich ascites tumor cells[74]. They also occur inside the cell[70,71] and may actually be obvious from the existence of sub-cellular organelles.

The expression means that unless metabolism proceeds at a certain rate, τ will increase, and the probability of interaction between the two enzymes decrease, allowing for other interactions, for example between k and m. At the same time, the parameter c_k may increase. Therefore, eq. (2) allows for extinction of metabolic pathways which are not used, or which are inhibited by end products, and for their replacement by a stage of metabolic 'trial and error', which includes increased access to DNA of previously caged or consumed metabolites. This is compatible with the finding that the number of enzymic sites often exceeds that of the appropriate metabolites in the animal cell[71].

The expression in eq. (2) describes that interactive enzymic structures are maintained by the ongoing metabolism and, in particular, if the metabolized substances are qualitatively identical and there is no accumulation of inhibitory end products, that the same structures are maintained for a long time. This may be evidenced, for example, by the increasing structuredness of the cytoplasmic matrix as the cell cycle proceeds[75]. It is also commonly observed in the constant internal environment of an organism (or cell culture dish) that the flux of metabolites occurs in well-defined morphological structures within the stationary cell, as opposed to the case of a proliferating cell. These structures often extend to neighboring cells through holes in the plasma membrane (tight junctions[76-79]) providing means of enzymic interactions beyond the cellular hierarchy (elementary reductionism[62]). They are broken down if the cellular communication with the surrounding fluids is changed, for example by a perturbation of the cellular envelope[34,35,80] prior to division or prior to DNA synthesis.

A further modification of the conditions may be that the two interacting enzymes are held together by covalent bonds which, of course, will slow down the decay of the probability of interaction relative to the case of enzymes that are only held together by weak hydrogen bonds or forces that are dependent on metabolism[72]. This could be expressed in terms of a decreased association parameter.

Empirical support for the idea that eq. (2) can describe cellular metabolism comes from the fact that tumorous and proliferating cells have a less distinct morphology than do stationary cells[36-44,59,60,81-83]. Eqs. (1) and (2) essentially conform to the corresponding equations regulating cognitive processes[63] and this also holds for the association parameter, A, given in eq. (2). A is given by the logarithm of the inverse of the iterated previous interactions between different elements within the appropriate enzymic concept times a constant[63], implying here that a multi-enzyme cluster or an organelle which has been used many times is stable. There is no experimental evidence in support of this on a quantitative basis, but this definition of A provides an interesting starting point for further descriptive analysis not only of the metabolic stability described above but also of the stabilization of metabolic pathways during the course of the evolution of the species.

Rate of the cognitive process and of metabolism

The rate of the entire metabolic cognitive process, $q/\Delta t$, i.e. the flow of metabolic 'attention' along the enzymic constellations of Q_X and Q_D provided by the genome, under permissive nutritive conditions, and in the absence of delaying metabolic iterations, is proportional to the rate of metabolism, which equals the number of enzymic interactions per unit time. This means that under permissive nutritive conditions, a higher rate of metabolism favors a more rapid cell proliferation, something which is commonly observed, for example

List of metabolic events that can be interpreted to represent increased flux rates and/or increased rate of molecular interactions, and that are commonly associated with proliferating cells relative to their stationary counterparts

Entry of calcium ions
Sodium-proton exchange (antiport)
Actomyosin contraction (motility)
Phosphoinositide turnover
Activation of the sodium and potassium -stimulated ATPase
Amino acid transport (sodium symport)
Glucose transport followed by glycolysis
Increased glycolysis at the plasma membrane
Increased oxidation-reduction
Increased fluidity of membrane lipid
Increased operation of membrane ATPases

in the increased heat generation of tumor cells, hyperplasia of tissue that is used, etc.

The increase of metabolism and increased heat production of proliferating cells is related to increased randomness also from the view-point of classical thermodynamics, namely in terms of entropy. Increased randomness is a feature commonly observed in tumor cells. The less differentiated they are, both in terms of morphology and metabolism, the more advantage they have relative to other cells in the same organism, the metabolism of which is directed towards iterations[44]. This observation cannot easily be explained in terms of irreversible thermodynamics. However, based on cognitive processes, morphological disorder, constituting evidence of metabolic randomness, would favor cell proliferation based on the reasonable assumption that the presence of a diversified pool of metabolites, acting as desuppressors of operons, increases the likelihood that iterative metabolic events will be replaced by ones favoring metabolic evolution. Each enzymic pathway is characterized by its influx of metabolites, $q_n/\Delta t$, and rate of iteration, which equals the number of end product metabolites formed, denoted $n_n/\Delta t$. These, in their turn, mediate other enzymic interactions and interactions with DNA. There is not necessarily equality between q_n and n_n since some metabolites may escape the chain of enzymes before they are fully converted. Therefore, $n_n/\Delta t$ equals the product of the probabilities of interaction between the N preceding enzymes in that particular pathway:

$$n_n/\Delta t = q_n/\Delta t \prod_{1}^{N} p_{kl} \qquad (3)$$

These probabilities are given by equations of the same type as eq. (2).

Then, of course, there is a sum of input metabolites and a sum of output metabolites, such that:

$$\Sigma n_n/\Delta t = \Sigma q_n/\Delta t \prod_{1}^{N} p_{kl} \qquad (4)$$

$\Sigma q_n/\Delta t$ is close to the rate of cellular transport of various metabolites to be converted in a cell, but may also depend on various forms of storage of chemical or other forms of energy, for example glycogen, lipid, ion gradients, gradients of pH and of charges. $\Sigma n_n/\Delta t$, on the other hand, lies close to the purpose of cellular life, which is anabolism aiming at self replication. $\Sigma n_n/\Delta t$ is a function not only of the rate of transport but also of the number of copies of enzyme and consequently reflects the stage of anabolism and maturity preceding commitment to division. Under permissive nutritive conditions, this quantity is proportional to the rate of evolution of the metabolic cognitive process, $q/\Delta t$:

$$q/\Delta t = K_1 \Sigma n_n/\Delta t \qquad (5)$$

where K_1 is a constant, reflecting the fact that biological cells tend to maintain their size. Another quantity of interest is $n/\Delta t$, the rate of appearance of new end-product metabolites. This rate is also proportional to the actual rate of metabolic evolution, $q/\Delta t$:

$$q/\Delta t = K_2 n/\Delta t \qquad (6)$$

where K_2 is another constant. This is to say that the type of end products of metabolism changes continuously and it is this change of quality rather than the quantity expressed in eq. (5) which brings about the desuppression of more operons. Eq. (6) affords considerable flexibility to account for the fact that the rate of progression through the cell cycle may not depend straightforwardly on the growth of cell mass. In some cases, the timing of cell division is determined in the preceding cell generations[6,8,45], which may be described by:

$$K_2 = f(t, K_1) \qquad (7)$$

where f is a function which varies with the nutritive conditions.

Also empirically, end product metabolites are important in cellular life, as illustrated by e.g. ATP, GTP, cAMP, pyruvate and lactate. A key metabolite is pyruvate, the end product of glycolysis, which can enter either fermentation, the citric acid cycle, amino acid synthesis (anabolism) or the synthesis of complex carbohydrates. Leakage of end-product metabolites may be associated with a withdrawal from further division[84]. Some end-product metabolites have been directly implicated in the commitment to DNA synthesis[85,86]. The expression in (5), though compatible with empirical observations, is difficult to understand at the molecular level while the expression in (6) can be interpreted as representing the successive desuppression of operons by newly formed end-products. The formation of new elements as a consequence of iterative cycles as represented in (5) has previously been discussed in connection with the mutability of hypercycles[65]. It is also inherent in the time-dependent evolution of cognitive processes, when the probability of interaction between two elements becomes unity and a third element is formed[63]. This is a process which is linearly related to time. At the molecular level, an explanation would have to be found in the interplay between the genome and the cytoplasm.

Modulation of metabolic rate

The main metabolic responses which serve the survival of the cell are catabolism, movement, sporulation, anabolism, and cellular (or nuclear) division (fig. 1). Of these, transport and catabolism occur more or less always, and are the basic elements of the process which have to exist before the other pathways are engaged. Metabolic evolution towards other pathways will occur if the rate of end-product formation is sufficient to activate more operons through desuppression. Therefore, as expressed by eqs. (4) and (5) cellular proliferation can be enhanced by an increased rate of transport of metabolites, and, as expressed by eq. (6) if metabolism is 'scrambled' in such a way that new end product metabolites further ahead in the chain of metabolic events arise. In agreement with this, an increased rate of transport of various metabolites seems to be the common denominator of action of several completely unrelated stimuli of division of stationary cells[9] such as serum[11,87,88], growth factors[24,29,88], or lectins[11]. The effect of an enhanced metabolism in speeding up cellular proliferation is also evident in the increased heat generation of tumor cells and in the hyperplasia of tissue which is used. Also the initiation of proliferation by lowered oxygen pressure[89,90] and the initiation of DNA synthesis by sustained depolarization[91–93] may fall into this category. In

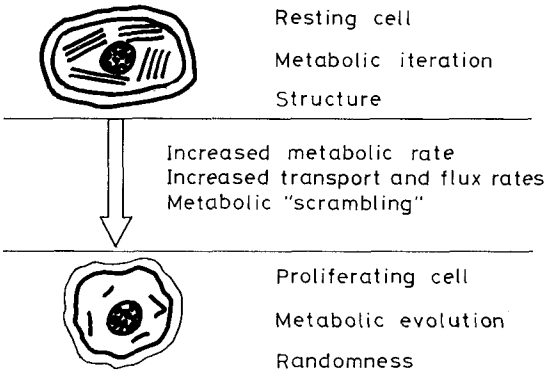

Figure 2. Illustration of the stationary and proliferating states of cellular metabolism and the connections between these states and morphology. As illustrated, a transition from the stationary state to the proliferating state can be brought about by increasing the rate of metabolism, or by increasing its diversity by other means (metabolic scrambling).

the former case, the switch to glycolysis and in the latter, the appearance of futile cycles can be interpreted as an increased diversity and rate of metabolism respectively. In some cases, however, a metabolic switch seems to be sufficient to initiate DNA synthesis[13, 94].

Some of the biochemical events that can be interpreted as increased flux rates and an increased number of interactions between molecules, and which are typical of proliferating cells, have been summarized in the table.

It is noteworthy that the effect of the increased transport of metabolites to induce cell division is reversible. In transformed cells (which are characterized by a continuous proteolytic breakdown of cell surface molecules[95]), division can be slowed down by adding certain macromolecules which are adsorbed to the cell surface[55–57], presumably physically blocking the transport of metabolites, or indirectly doing so by increasing the level of cyclic AMP[58–61]. This kind of treatment leads to restoration of a type of morphology which is typical of normal cells[55–57]. The combined effect of a decrease of the transport of certain metabolites and the appearance of a more well-defined morphology can also be brought about by the addition of cyclic AMP and some of its derivatives to proliferating cells[58–61, 96–99].

These data, which are representative of the huge literature in this field, provide a firm link between the transport of certain metabolites and cellular morphology such that in the majority of cases, there is an inverse relationship between the rate of transport of substances being metabolized and the amount of well defined structure in the animal cell. In some specialized tissue such as epithelium, most of the transported compounds escape metabolization. Another consequence of the presence of cAMP is often that specialized functions available on the genome of a particular cell are activated, for which reason this compound profoundly affects differentiation. The flux of metabolites may then be diverted from proliferation (or a stationary state) to these specialized functions (which may include controlled cell division) in such a way that the cells can carry out and iterate their specialized functions within the organism[100].

The above empirical findings, illustrated in figure 2, can be interpreted in terms of the formalism presented here and previously[63]. A necessary and reasonable[70, 71] postulate is that the enzymes act as volume elements and, as such, provide the basis of the visible cellular structures. Namely, in the resting cell, metabolism is concentrated on a few enzymic pathways where iteration of enzymic interactions according to eq. (2) increases the likelihood that the same interactions will occur again. On the one hand, the induction of new enzyme leads to an increased quotient of k_l/C_k, and on the other, compartmentation leads to the replacement of C_k by the smaller number c_k. This is descriptive, but also inherent in cognitive processes inasmuch as c_k decreases as a function of a decreasing association parameter[63]. When the frequency of interaction between k and l decreases, either by a decreased input of substrate to fuel the enzymic interaction, or by end-product inhibition on either k or l, this means that the time τ will increase and the metabolic and morphological structure will become more likely to dissolve. Therefore, the expression in eq. (2) in combination with those in eqs. (5) and (6) have morphological implications which conform with empirical findings in that proliferating cells are characterized by a more random morphology than stationary cells, with few exceptions, and that a switch to the proliferating state can be brought about by increasing the rate of metabolism (fig. 2). A most common way to do this is via a perturbation of the plasma membrane, this organelle being the key to the release of topo-inhibition or contact inhibition of transport, growth and movement. A second possibility for achieving this is by forcibly dissolving metabolic structures and compartments in order for the possibilities of interactions within enzymes and with the genome to become more diversified. This is equivalent to the randomness which is the charter that gives the proliferating cell its advantage, and is best linked to the evolution of the metabolic process as described in eq. (6).

In summary, the treatment of metabolism as a 'cognitive process' is useful for understanding qualitative relationships between the rate of transport of metabolites, metabolic iteration in stable phenotypes, morphology, and metabolic evolution in proliferating cells (fig. 2). Even though the treatment may be incomplete or incorrect in some respects, it is noteworthy that physical life may be a thermodynamic and a cognitive process as well. The rapidly proliferating cell corresponds to an evolving string of cognitive elements while the stationary (or slowly proliferating) cell corresponds to thoughts that are iterated in a stable (and greedy) environment.

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