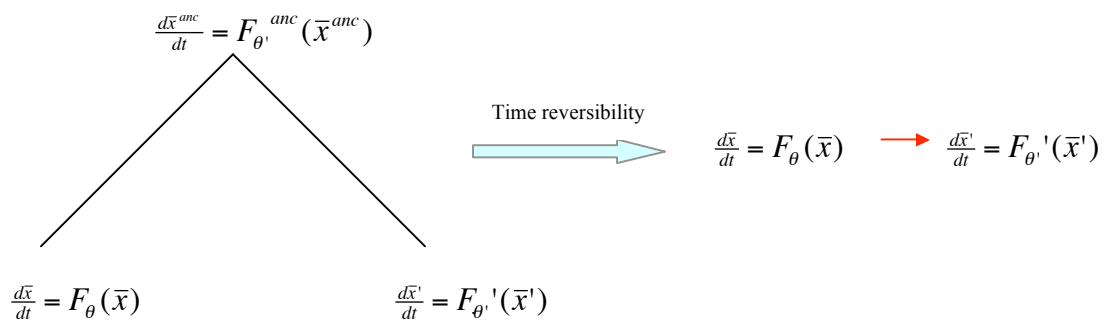


# *Evolving Dynamical Systems – case study: Cell Cycle*

17.7.07

The biosciences has recently seen the rise of two major trends. Firstly, the use of evolution in structural biology as seen in bioinformatics and comparative genomics. Secondly, the use of predictive mathematical modelling in systems biology and computational biology. Clearly, there is an intersection between these two major areas and it would belong to the field of comparative systems biology. We will here simplify fast to get to a simple well-defined problem. Two phylogenetically related dynamical systems used to describe two homologous biological systems. Such a relationship could place constraints on which kinds of models you could use. Very often you demand certain kinds of stability of the model and now you would have to demand that all ancestral intermediates are also stable. This could place constraints on which order you could remove/add/modify components.

A great variety of models are used to describe the dynamics of biological systems. Such models can be discrete/continuous time, stochastic/deterministic, discrete/continuous space and further refinements can apply. We will focus on a simple widely applicable kind of model, where there already is a well established and successful application. Ordinary differential equations (ODEs) is such a class of modeling and the cell cycle has a series of successful ODE-models attached to it.



Models – abstract representations of biological systems - would also have to evolve as the system evolves. Here we have a model for the ancestral system –  $F^{anc}$  – that evolved into two systems observed in the present:  $F$  and  $F'$ . This view has practical consequences. If  $F$  was well known (parameterized), but  $F'$  not, it would be reasonable to transfer parameters from  $F$  to  $F'$ , possibly in the form of a Bayesian prior. Additionally it could also place constraints on which models would be worth considering as  $F$  and  $F'$  would have certain key properties (stability, robustness, oscillations,..) to be useable as models. But so would all evolutionary intermediates.

If the process of evolution is time reversible, then it can be assumed that the first dynamical system is an ancestor to the second.

**Linear Differential Equations - LDEs.** The simplest dynamical systems are linear differential equations, where a set of species  $\{x_1, x_2, \dots, x_n\}$  interacts and can be described by a set of linear equations:

$$X(0)=x, \quad X'(t)=QX(t) \quad - \quad \text{this is solved by } X(t)=e^{Qt}X(0)$$

LDEs are extremely useful as local approximations to more complicated ODEs, so if the relevant dynamic trajectories are close to a stable equilibrium point and the evolution of the dynamical system is sufficiently regular, then this class of equations are fully valid. However, biological evolution often involves addition/deletion of components/interaction and drastic parameter changes. It depends on the evolutionary distance in question.

**Kinetic and Regulatory Equations - KREs.** The time rate of change of components will be described by ordinary differential equations. These equations take into account synthesis and degradation of components, and activation and inactivation of the regulatory components. Each term in the equations represents a particular reaction in the network. The kinetic terms follow the law of mass action or Michaelis-Menten kinetics for the catalyzed reactions. A loop-up table for the kinetic terms can constructed based on the published cell cycle models.

**Models of System Evolution.** A simple model describing **LDE** evolution would be that species can be added and deleted and interactions modified. This also implies that in the evolutionary intermediates could exist not observed in the observed present systems. A simple model for such a dynamical system would be:

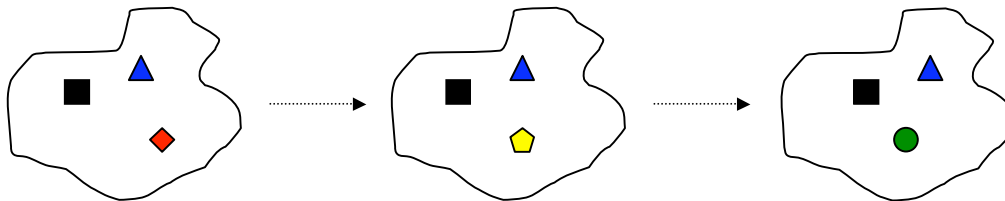
- Species can be added with rate  $\lambda$  and each species can be deleted with rate  $\mu$ . When a new species is added, it is new and will randomly interact with an existing specie with probability  $p$  and if it interacts its interaction is chosen from a normal distribution.

- Interactions  $q_{ij}$  evolve according to the Ornstein-Uhlenbeck process, which conveniently has a normal equilibrium distribution.

The simplest models for the evolution of *KREs* would be the heart of the eukaryotic cell cycle machinery. This is based on the antagonistic interaction of Cdk1/CyB complex and its degradation machinery (Cdh1/APC). This antagonistic relationship creates an irreversible switch with two characteristically different levels Cyclin-B levels. A negative feedback loop helps the cells to move around this irreversible switch which result an oscillation in CycB levels. This core of the eukaryotic cell cycle control system has evolved further by additional components. In present day eukaryotes, the cell cycle control networks are similar but not identical.

**Adding Selection.** The dynamic system must have certain features to be useful to the organism and as the system evolve it must be possible to add selection so dynamical systems without those features are out of bounds. For the eukaryotic cell cycle system, the concentration of Cdk1/Cyclin-B complex is the most obvious choice to follow. If the level of Cdk1/cycB is oscillating between zero and arbitrary chosen high values then the cell can proliferate. If the concentration of Cdk1/CycB cannot cross certain thresholds, then the cell will stop proliferating and will be over-grown by other ‘mutants’.

The questions one would like to address in any analysis of the evolution of a dynamical system is the same as for evolutionary analysis of other “homologous objects”: What are the parameters of the evolutionary process? What have been the intermediate dynamical systems? What are the features that evolution has conserved? These are clearly worthwhile to answer, but there are likely to be practical problems associated. In contrast to for instance sequence data, it is unlikely that one can observe thousands of dynamical systems, each to high degree of precision. If one is lucky, one has two systems, each observed with a high degree of error. Additionally, researchers often borrow parametrisations from other species, so it would not even be clear, which system is which system. (We might need a concept of “system recombination”!!!) Despite these issues, the problem could well be of great use. For instance, if one dynamical system was very well characterized and we wanted to transfer that model with parameters to another species, then an evolutionary model would be needed. A less model based question would be: Given two dynamical systems, what are their similarities and differences?



In this little cartoon, we first have 3 components interacting. At some intermediate stage one component has been gained, another lost. In the final system it has happened again. Only the first and the last system can be observed, so statements concerning intermediate dynamical systems must be inferred using a model of evolution.

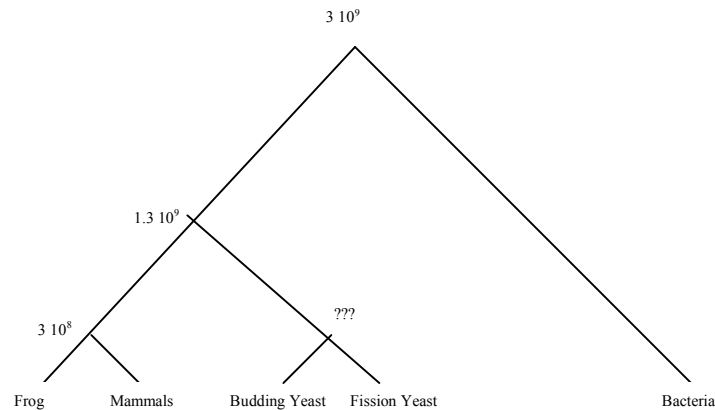
**Selection, Conservation and Comparison of Dynamical Systems.** When a series of dynamical systems have been observed a series of questions will be of immediate interest that are common to any comparative study. The moment we have an evolutionary model then questions of selection and conservation can be addressed. At times it there can be a given a description of which features are essential, such as oscillatory behaviour in the cell cycle. Often different components in the dynamical systems can be identified to each other through homology, ie similar proteins have had the same function through time back to a common ancestor. However, “function sliding” is known from other systems, where the evolution of roles has occurred and is of high interest, when it happens.

**MCMC integration over evolutionary histories.** In applying this to the simplest case – two homologous systems – their joint probability must be calculated, ie  $P_{\theta}(D_1)P_{\theta}(D_1 \rightarrow D_2)$ , the evolutionary process is time reversible.  $P_{\theta}(D_1)$  is the equilibrium distribution of the evolutionary process and  $P_{\theta}(D_1 \rightarrow D_2)$ , the probability that  $D_1$  evolves into  $D_2$ . These quantities are hard to calculate analytically, but can be estimated by MCMC. This has some similarity to earlier projects done by Eleni Giannoulatou and Aziz Mithani, who should be consulted.

It is clear that this is a hard problem and a temporary solution could be to use parsimony (find the cheapest evolutionary path). In this case it would involve removing/adding components and changing parameters. The score function would thus have 2 components a discrete and a continuous. This criteria would probably be augmented with some common sense criteria demanding that the intermediate dynamical systems are functional.

**Application Example: The Cell Cycle** The application areas for this area are many fold, but it also immediately becomes more complicated in that equations will not stay linear and data are rarely ideal. Since this is a very general problem and many examples could be found. However, the systems must have certain properties to be useful: They must be homologous, but must have evolved enough not to be identical and not so much that they aren’t comparable. Additionally, the knowledge of each system must be sufficient to make them differ across species, ie all the difference must not just be in a noisy characterisation, so one might just as well use the frog model in mouse and visa versa. We here describe the models used for the cell-cycle.

Three cell cycle control network will be studied: the core mechanism described above, and the network controlling the cell cycle of budding and fission yeasts. Both yeasts have Cdk inhibitors in order make the bistable switch more robust. This is a similarity between them. On the other hand, they have dissimilarities as well. Budding yeast cell cycle depends on Cdk1 complexes with cyclins different from the B-type. In contrast, fission yeast uses intensively a novel mechanism to inhibit the Cdk1/CycB complex which is not very much used in budding yeast. This similarities and differences make these two yeasts ample examples to study the evolution of the fundamental biological regulatory network.



Mitotic control is well studied in the following organisms: Fission Yeast (*Schizosaccharomyces pombe*), Budding Yeast (*Saccharomyces cerevisiae*), Frog (*Xenopus laevis*), Mammals and Bacteria.

**Project Plan** – it is describes as an 8 week project, but it could clearly be made slightly longer and more easily much longer. Other models systems could be analyzed, more homologous variants could be observed, more serious data analysis could be attempted.

- Week 1 Read the basic literature.
- Weeks 2-3 Write LDE and KRE evolver
- Week 4 investigate evolution of dynamic systems describing the cell cycle by varying selection criteria and evolutionary rates. Start simulations in different known dynamical systems.
- Weeks 5-7 Given 2 CCDs calculate their joint probability using MCMC. Estimate evolutionary parameters.
- Week 8 Writing the report is encouraged to be done continuously, but the last week will almost have full focus on this.

*Note of caution:* This is project is highly idealized in the sense that it is hard to observe models and have major uncertainty associated which could be much larger than the variance introduced by the evolutionary process. Nevertheless this kind of model are likely to be of increasing importance as models become ubiquitous in the biosciences.

*Nature of the project:* It demands solid numerical and programming skills, the ability to read the modelling literature. It easily scales to a full PhD project by including more complex models, proper data analysis and modelling more than 2 dynamical systems.

### **References**

- Brahnik, P and JJ Tyson (2006) "Cell Cycle Control in Bacteria and Yeast" *Cell Cycle* 5.5:22-29.  
 Csikasz-Nagy, A et al. (2006) "Analysis of a Generic Model of Eukaryotic Cell-Cycle Regulation" *Biophys. J.* 90.4361-79 + online material  
 Goldbeter, A (1996) "Biochemical Oscillations and Cellular Rhythms" CUP chapt. 10  
 Hirsch, Smale and Devaney (2003) "Differential Equations, Dynamical Systems, and an Introduction to Chaos" Academic Press  
 Morgan, D.O (2006) "The Cell Cycle" OUP  
 Novak, B et al.(1998) "Model scenarios for evolution of the eukaryotic cell cycle" *Phil.Trans.B.Sco.Lond. B.* 353.2063-76.