I. Dynamics of living systems

- Understanding the dynamics at the **molecular** level.
- Understanding the dynamics at the **cellular** level.
- Filling the gap between these two levels.

**Dynamics ↔ Function**

"The complexity pyramid might not be specific only to cells."

Different levels of structural organization:

<table>
<thead>
<tr>
<th>Residues</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^2$</td>
<td>1</td>
</tr>
<tr>
<td>$10^5$</td>
<td>2-10</td>
</tr>
<tr>
<td>$10^8$</td>
<td>10-100</td>
</tr>
</tbody>
</table>

Large structures

- **Ribosomal functional complexes**
  (Cate, Yusupov, Yusupova, Earnest & Noller, Science 1999, 285, 2095).
- Complexes formed by several proteins, cascades of interactions.
Computational models & methods for:

- Large assemblies, complexes of proteins
- Membranes and cytosolic fibrous systems
- Cellular pathways. Signaling & regulation of cell cycle

**Bridging the gap**

between

**Molecular and Cellular scales**

- What is the optimal (realistic, but computationally efficient) model for a given scale (length and time) of representation?
- Which level of details is needed for representing global (collective) motions?
- How much specificity we need for modeling large scale systems and/or motions?
- What should be the minimal ingredients of a simplified (reductionist) model?
Cellular pathways are usually described by simple Mass-Action Kinetics.

ATM signaling

P53 regulation

DNA damage signaling pathways

Computational challenges

- Realistic modeling of the space-time dependence of cellular processes
- Multiscale representations of structure/dynamics
- Extracting rules from microscopic simulations, for macroscopic approaches
- Bridging between continuous and discrete models

Systems Biology

There is not yet consensus on what systems biology actually is:

“The analysis of networks, regulation, how the things work from a whole-system point of view” Sauro

“physiology of cells” Adam Arkin

“mathematical modeling of biological systems” Schneider

Extensive usage of math and computations

An old concept that became popular with:
- the sequencing of the human genome
- genomics, proteomics, metabolomics concepts
- microarray technologies, instrumentation that allow for high throughput measurement of DNA, RNA and proteins – global data sets
Combination of computations, experiments and theory is vital.
Modeling is an integral part of systems biology building the networks of interactions and examining its dynamics.
Top-down approach (for modeling diseases, subcellular processes – apoptosis, or entire ‘silicon cells’).
Most of the info/data needed for modeling is in the text of scientific literature, not in databases or equations.
Has potential to impact drug discovery and development timeline (focus on the connection between molecular and physiological).

A shift from “list of genes” or “proteins” to “structure” and “dynamics”

Three components of the computational approach:
- System structure (network of gene interactions, biochemical pathways, etc.)
- Properties of the components (reactivities, binding affinities, etc.)
- System dynamics (sensitivity analysis, bifurcation analysis)

System = Genome, proteome, metabolome, etc.


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Mathematical Modeling of Cellular Networks

Where transition (or jump) probabilities between states control the probabilistic evolution of states. Closely associated are the eigenvector associated with the smallest eigenvalue extracts the slowest (or least probable) passage.

Methods for simplifying and reducing complex models essentially rely on the difference in time and spatial scales, often through abstraction.

2. Define the scope and abstraction level of the model, which depends on the available knowledge. Lack of quantitative data on rate constants, concentrations.

3. Robustness is an essential property, which may be induced by adaptation, parameter insensitivity, negative feedback loops or feed-forward control mechanisms, structural stability or modularity.

Kirchhoff/connectivity matrix is analogous to the Transition Rate Matrix of Master Equation Formalism

Applications to macromolecular dynamics:
- Rotational dynamics of polymers (DREIS)
- Folding dynamics of model proteins

To ensure that the important details are not being neglected.
- To be able to construct simplified models that are quantitative, rather than just qualitative.
How to analyze the time evolution of macrostates?

- **Master Equation formalism**
- \( \frac{dP(t)}{dt} = AP(t) \)
- **Formal solution:**
  \[
  P(t) = \exp\left\{ -A t \right\} P(0) = B \exp\left\{ L^{-1} \right\} B^{-1} P(0)
  \] (transition probability matrix)

Classical kinetic modelling of protein folding/unfolding

Two-state transition

The simplest type of transition between states \( U \) and \( N \) is a two-state process, given by the scheme

\[
\begin{align*}
U & \xrightarrow{k_f} N \\
N & \xleftarrow{k_u} U
\end{align*}
\]

The differential rate expressions holding in this case are

\[
\begin{align*}
\frac{d[U]}{dt} &= -k_f[U] + k_u[N] \\
\frac{d[N]}{dt} &= +k_f[U] - k_u[N]
\end{align*}
\]

where \([U]\) and \([N]\) are the instantaneous (time-dependent) concentrations of the unfolded and folded conformations, respectively, and \(k_f\) and \(k_u\) are the folding and unfolding rate constants.

Initial concentrations = \([U]_0\) and \([N]_0\).

In folding experiments, we take \([N]_0 = 0\), and the instantaneous concentration \([N]\) is given by

\[
[N] = [U]_0 - [U]
\]

such that the differential folding equation reduces to a non-homogeneous, first order differential equation

\[
\frac{d[U]}{dt} = -(k_f + k_u)[U] + k_u[U]
\]

The solution is:

\[
\frac{[U]}{[U]_0} = \frac{k_u}{k_u + k_f} + \frac{k_f}{k_f + k_u} \exp\left\{ -(k_f + k_u)t \right\}
\]

The equilibrium concentrations define the equilibrium constant for the folding reaction

\[
K_{UN} = \frac{[N]_\infty}{[U]_\infty} = \frac{k_f}{k_u}
\]

The equilibrium constant is related to the free energy of unfolding by the equation

\[
\Delta G_{UN} = -RT \ln K_{UN}
\]

Several proteins have been observed to obey such a two-state transitions.
Sequential transition from U to N

The transition from U to N has been shown in numerous examples above to proceed through the formation of one or more intermediates.

Let us consider here the simpler case of a single intermediate. Let \( k_{XY} \) designate the rate constant for the passage from state \( X \) to state \( Y \). Using this notation,

\[
\begin{align*}
k_{UI} & \to I \\
k_{IN} & \to N
\end{align*}
\]

The set of equations for the differential change

\[
\begin{align*}
\frac{d[U]}{dt} & = -k_{UI} [U] + k_{IU} [I] \\
\frac{d[I]}{dt} & = k_{UI} [U] - k_{IU} [I] - k_{IN} [I] + k_{NI} [N] \\
\frac{d[N]}{dt} & = k_{IN} [I] - k_{NI} [N]
\end{align*}
\]

In concise notation,

\[
\frac{dX(t)}{dt} = A X(t)
\]

where \( X(t) \) is the vector of the instantaneous concentrations, and \( A \) is the matrix of rate constants, shortly referred to as a rate matrix. This matrix equation is similar in form to a master equation, where concentrations are replaced by probabilities.

The set of coupled differential equations is conveniently found by matrix algebra methods, using the similarity transformation

\[
A = B \Lambda B^{-1}
\]

Here \( B \) is the matrix of eigenvectors of \( A \), and \( \Lambda \) is the diagonal matrix of eigenvalues. The instantaneous concentrations/probabilities are controlled by

\[
X(t) = B \exp \{ t \Lambda \} B^{-1} X(0)
\]

This equation may be rewritten in explicit notation for each state \( i (i = [U], [I] \text{ or } [N]) \) as

\[
x_i(t) = \sum_j \sum_k B_{ik} \exp \{ \lambda_k t \} B^{-1}_{kj} x_j(0)
\]

where the subscript denote the particular elements of the matrices, or vectors, and the summations are carried over all elements.

The last equation is similar in form to the multieponential form generally postulated for describing complex processes.