Slide 1

Computational Systems Neurobiology

Nicolas Le Novère, EMBL-EBI

Slide 2

European Bioinformatics Institute

British outstation of the European Molecular Biology Laboratory

- Databases
  - Sequences, structures
  - Transcriptomics, Proteomics
  - Controlled vocabularies and dictionaries

- Research groups
  - Comparative genomics (Ouzounis)
    Structural Genomics (Thornton)
    Molecular Evolution (Goldman)
  - Text-Mining (Rebholz-Schumman)
    Computational Systems Biology (Le Novère)
    Statistical array analysis (Huber)
    Genomic analysis of regulatory systems (Luscombe)

Marie Curie Training site Fellowships: 3-6 months. Fully funded.

EMBL e! Ensembl UniProt

IntAct R ?

GO ChEBI InterPro IntEnz

Slide 3

Computer simulation Vs. mathematical models

One would like to be able to follow this more general process mathematically also. The difficulties are, however, such that one cannot hope to have any very embracing theory of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis.

A. M. Turing (1952). The chemical basis of morphogenesis. *Phyl Trans Roy Soc Lond* B237: 37-72

[About the development from one developmental pattern to another, a non-linear process]

Slide 4

Simulation in Neurobiology

Hodgkin and Huxley
"A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve". *J Physiol* 1952, 117: 500-544

Rall
"Branching dendritic trees and motoneuron membrane resistivity". Exp Neurol 1959, 1: 491-527

[NEURON] Hines
"A program for simulation of nerve equations with branching geometries". Int J Biomed Comput 1989, 24:55-68

[GENESIS] Wilson, Bhalla, Uhley, Bower
"GENESIS : A system for simulating neural networks." Advances in neural information processing systems. Touretzky, D. ed, 1989, pp. 485-492

Land, Salpeter, Salpeter
"Kinetic parameters for acetylcholine interaction in intact neuromuscular junction". Proc Natl Acad Sci USA 1981, 78:7200-7204

[MCell] Bartol, Land, Salpeter, Salpeter
"Monte Carlo simulation of miniature endplate current generation in the vertebrate neuromuscular junction". Biophy J 1991, 59: 1290-1307

Changeux, Courrège, Danchin
"A theory of the epigenesis of neural networks by selective stabilization of synapses". Proc Natl Acad Sci USA 1973, 70: 2974-2978

Tsodyks and Markram
"The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability". Proc Natl Acad Sci USA 1997, 94: 719-723

Slide 5

the Medium Spiny Neuron of the striatum

Axon

Slide 6

Kinetic model of receptor function

Edelstein et al. (1996) *Biol Cybern*, 75: 361-379

Excitatory post-synaptic potential

Le Novère and Shimizu (2001)
Bioinformatics 17: 575-576

Movie Purkinge

Compartmental models

De Schuter and Bower (1994) *J Neurophysio*, 71: 375-419

Multiple afferent signals

Fundamental Neuroscience
Squire et al. 2rd ed(2003)

Dopamine mesotelencephalic pathway

Glu
GABA
DA

Neocortex

Striatum

GPe

Subthalamic nucleus

SNc

GPi/SNr

Thalamus

Voluntary motion
Emotional control
Reward
Learning

Parkinson's
Huntington
Drug addiction
Schizophrenia

Dopamine mesotelencephalic pathway

cortex frontal

striatum

mésencéphale ventral

DARPP-32, a signal integrator

Model of DARPP-32 regulation

Upinder Bhalla

Negative loops: "russian dolls"

Choose the right formalism

$$E+S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \underset{kcat'}{\overset{kcat}{\rightleftharpoons}} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E+P \qquad \frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

$$E+S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \overset{kcat}{\longrightarrow} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E+P \qquad \text{catalysis irreversible}$$

$$E+S \underset{ksd}{\overset{ksa}{\rightleftharpoons}} ES \overset{kcat}{\longrightarrow} E+P \qquad \begin{array}{l}\text{product is consumed}\\ \text{before rebinding}\end{array}$$

$$S \overset{E}{\smile} P \qquad \text{steady-state} \qquad \frac{d[P]}{dt} = \frac{[E]\,kcat}{Km}$$
$$1 + \frac{Km}{[S]}$$

Leonor Michaelis, Maud Menten (**1913**).
Die Kinetik der Invertinwerkung, Biochem. Z. 49:333-369.

G. E. Briggs and J. B. S. Haldane (**1925**)
A note on the kinetics of enzyme action, Biochem. J., 19, 339-339.

Signal Transduction ≠ Metabolic Control

- Signal transduction and steady-state are contradictory.

- Enzyme, substrate, product are proteins:
  - [S] ~ [E], [E] not constant
  - Rebinding of product is not negligible.

- Approximations are context-dependant: Model composition becomes questionable (validity of the assumptions), or even impossible (no explicit representation of some species).

- Michaelis-Menten is an approximation meant to ease analytical work. In most cases we don't need it anymore, and should use elementary steps, representing all molecular species.
  - computers do (part of) the job for you!

The complete model

57 species, 104 reactions

- D + CDK5 • D_CDK5 • D75 + CDK5
- D75 + PP2A • D75_PP2A • D + PP2A
- D75 + PP2AP • D75_PP2AP • D + PP2AP
- D137 + CDK5 • D137_CDK5 • D75-137 + CDK5
- D75-137 + PP2A • D75-137_PP2A • D137 + PP2A
- D75-137 + PP2AP • D75-137_PP2AP • D137 + PP2AP
- D34 + CDK5 • D34_CDK5 • D34-75 + CDK5
- D34-75 + PP2A • D34-75_PP2A • D34 + PP2A
- D34-75 + PP2AP • D34-75_PP2AP • D34 + PP2AP
- D34-137 + CDK5 • D34-137_CDK5 • D34-75_137 + CDK5
- D34-75-137 + PP2A • D34-75-137_PP2A • D34-137 + PP2A
- D34-75-137 + PP2AP • D34-75-137_PP2AP • D34-137 + PP2AP

- D + CK1 • D_CK1 • D137 + CK1
- D137 + PP2C • D137_PP2C • D + PP2C
- D75 + CK1 • D75_CK1 • D75-137 + CK1
- D75-137 + PP2C • D75-137_PP2C • D75 + PP2C
- D34 + CK1 • D34_CK1 • D34-137 + CK1
- D34-75 + PP2C • D34-75_PP2C • D75 + PP2C
- D34-75 + CK1 • D34-75_CK1 • D34-75-137 + CK1
- D34-75-137 + PP2C • D34-75-137_PP2C • D34-75 + PP2C

- D + PKA • D_PKA • D34 + PKA
- D34 + PP2B • D34_PP2B • D + PP2B
- D75 + PKA • D75_PKA • D34-75 + PKA
- D34-75 + PP2B • D34-75_PP2B • D75 + PP2B
- D137 + PKA • D137_PKA • D34-137 + PKA
- D75-137 + PKA • D75-137_PKA • D34-75-137 + PKA

- CK1 + CK1 • CK1_CK1 • CK1P + CK1
- CK1P + PP2B • CK1P_PP2B • CK1 + PP2B

- D75 + PKA • D75_PKA
- D34-75 + PKA • D34-75_PKA
- D34-75-137 + PKA • D34-75-137_PKA

- R2_PKA2 + cAMP • cAMP_R2_PKA2
- cAMP_R2_PKA2 + cAMP • cAMP2_R2_PKA2
- cAMP2_R2_PKA2 + cAMP • cAMP3_R2_PKA2
- cAMP3_R2_PKA2 + cAMP • cAMP4_R2_PKA2
- cAMP4_R2_PKA2 • cAMP4_R2_PKA + PKA
- cAMP4_R2_PKA • cAMP4_R2 + PKA

3

Effect of CDK5 activity

A   B   C

· Takahashi S, Ohshima T, Cho A, Sreenath T, Iadarola MJ, Pant HC, Kim Y, Nairn AC, Brady RO, Greengard P, Kulkarni AB. Increased activity of cyclin-dependent kinase 5 leads to attenuation of cocaine-mediated dopamine signaling. *Proc Natl Acad Sci USA*. 2005 [Epub ahead of print]

Classical view of the synapse

· One kind of transmitter
· One kind of receptor
· Homogenous distribution
· Frozen in space and time

Structural complexity

Atlas of Ultrastructural Neurocytology
http://synapses.mcg.edu/atlas/eurosci

Shoop et al. (2002)
J Neurosci, 22: 748–756

Movie NMJ

The position of receptors affects the signal

A

B   C

Open AMPARs — Circular PSD, Rectangular PSD, Annular PSD

Time (ms)

CV — Circular PSD, Rectangular PSD, Annular PSD

Franks et al. (2003) *J Neurosci, 23: 3186–3195*

Complex post-synaptic machinery

Husi & Grant (2001) *TINS, 24: 259–266*

Receptors for neurotransmitters are moving

Barry and Ziff. (2002)
Curr Opin Neurobiol, 12: 279–286

Choquet & Triller (2003)
Nat Rev Neurosci, 4: 251–265

DopaNet — The Meso-Telencephalic Dopamine Consortium

Systems Biology of Neuroadaptation in Mesotelencephalic Dopamine Pathways

EMBL-EBI — European Bioinformatics Institute

Speakers
Keynote Speaker
Professor J. Paul Bolam, MRC Anatomical Pharmacology Unit, Oxford, UK

Synaptic plasticity and diversity of electrophysiological responses
Stephen Fitzjohn, MRC Center for Synaptic Plasticity, UK
Mark Ungless, University of Oxford, UK
Stephane Charpier, Collège de France, France
Kevin Gurney, University of Sheffield, UK

From the receptors to the molecular targets
Eric Fernandez, EMBL-EBI, UK
Kerstin Håkansson, Karolinska Institute, Sweden
Emmanuel Valjent, INSERM, France

Genetics of cellular plasticity
Peter Vanhoutte, Universite Pierre et Marie Curie, France
Birgit Liss, Philipps University Marburg, Germany
Sabine Spijker, Free University of Amsterdam, Netherlands

Venue Information
Lille Grand Palais
1, Bd des Cités Unies
59777 EuraLille,
Lille, FRANCE
On 17 May 2006. From 08:45-17:30

Organisers
Nicolas Le Novère
Jean-Antoine Girault
Marie-Claude Potier

The meeting is open to everyone. Students of DopaNet teams are eligible for a refunding of their travel and accommodation expenses.

The Webpage
http://www.ebi.ac.uk/compneur-srv/dopanet/dopaneteDay.php

Sponsored by
EUROPEAN SCIENCE FOUNDATION

Multi-scale multi-algorithm problem

EMBL-EBI

Whole-neuron
Cable theory
$1\mu m$-$1m$
$1ms$-$1week$

Signaling network
ODE
$1\mu m$-$10\mu m$
$1s$-$1d$

Synapse
Stochastic algorithm
$1nm$-$100nm$
$1\mu s$-$1ms$

Dendritic spine
Diffusion, PDE
$100nm$-$1\mu m$
$1ms$-$1s$

Modelisation: the collaborative approach

EMBL-EBI

deterministic — stochastic

VCell
GENESIS

E-Cell

MesoRD
SmartCell

MCell
StochSim

Whole-cell

Copasi

Jarnac

SBW
BioSPICE
NEOSIM

CellDesigner

DB interface

KEGG
Reactome

GRID, RPC

All these programs speak SBML
(Systems Biology Markup Language)

SBML

Systems Biology Markup Language

SBML

A Tool-Neutral Exchange Format
The Systems Biology Markup Language (SBML) is a computer-readable format for representing models of biochemical reaction networks. SBML is applicable to metabolic networks, cell-signaling pathways, regulatory networks, and many others.

Internationally Supported and Widely Used
SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is supported by over 60 software systems, including the following (where "*" indicates SBML support in development):

A Free and Open Language
Advances in biotechnology are leading to larger, more complex models. The systems biology community needs information standards if models are to be shared, evaluated and developed cooperatively. SBML's widespread adoption offers many benefits:

- Enabling the use of multiple tools without rewriting models for each tool
- Enabling models to be shared and published in a form other researchers can use even in a different software environment
- Ensuring the survival of models (and the intellectual effort put into them) beyond the lifetime of the software used to create them

Does Your Software Support SBML?

Requirements for mathematical models

EMBL-EBI

- Bench biologists need to find models relevant for their research.
- Modellers need to reuse existing models, or portions of models, rather than rewrite them from scratch. Model composition on a large scale will be possible only if we have such a model "shopping cart".
- But ...
  - No true database of models, only repositories, sometimes with side information.
  - few quality control on the models available online (JWS excepted).
  - No annotation of models: reactants are A, B, C, reactions 1, 2, 3 etc.
  - Lack of standards on production, curation and annotation of models.
- Biomodels.net: collaboration between Caltech, EMBL-EBI, SBI, JWS etc. etc.
  - SBML: Systems Biology Markup Language
  - MIRIAM:
    Minimum Information Requested In the Annotation of Models
  - Controlled vocabularies:
    - Parameters Kd, Ka, Kp, IC50 ARE DIFFERENT!
    - "Michaelis-Menten", "Mass Action Law" etc.
  - Biomodels database, a database of "Systems Biology Models"

Models repositories already exist

- SBML model repository [SBML]
- CellML models repository [CellML][curation][search]
- JWS online [SBML, Pysces][curation]
- E-Cell Developer Network [E-Cell, SBML]
- DOQCS [GENESIS][curation][search]
- SenseLab ModelDB [NEURON, GENESIS]
- …

Biomodels database

- Originally a collaboration between the EMBL-EBI, and SBML core team. Forthcoming collaborations: Keck Graduate Institute, EML, JWS plus X plus Y plus you.
- Each model served by the database will be published (submitted or in the press will be processed but kept private).
- To be accepted in biomodels, a model has to be semantically correct, i.e. when instanciated, provides values corresponding "well" to the results described in the publication.
- Model components are annotated: creator, publication, Gene Ontology, Taxonomy, Reactome, UniProt, KEGG, OMIM, ChEBI etc.
  - search for all models related to "synaptic plasticity", "Hodgkin" or "CALM_HUMAN"

Structure of Biomodels