

Dynamic Pathway Modeling of DNA damage Response System and Parameter Estimation

Li Zhang(lzhang1@uci.edu), Eric Mjolsness(emj@uci.edu)
Computer Science Department, Donald Bren School of Information and Computer Sciences
University of California, Irvine, California, U.S.A.

The development of computational models for systematic, large-scale biochemical networks is becoming an important part of modern research with scientific and practical value. Given a biochemical pathway structure and kinetic scheme, we can compute the time series of the system variables such as molecular concentrations and simulate the state of the system. We can use model as a tool to explain and predict the behavior of a biological system, or a tool for engineering and designing purpose. However, one major limitation in modeling dynamics of pathway is that many reaction constants/parameters are unavailable in the literature or are very difficult to be measured experimentally. Thus parameter estimation plays an important role in creating computational models in a systematic and efficient way.

The ionizing radiation (IR) in space characteristically has low dose-rate. IR is known to trigger the DNA damage response which is a biological defensive mechanism in eukaryotic cells to enhance the cellular resistance to the genotoxic effects by radiation. DNA double-strand-breaks (DSBs) are mainly caused by ionizing radiation or reactive oxygen intermediates. If this damage is not detected and handled in a timely manner, it will pose serious consequences to cells. Many studies have revealed that ataxia telangiectasia mutated kinase (ATM) plays a pivotal role in adapting this type of DNA damage sensing. It senses the damage and quickly activates the DNA damage response signaling cascades, phosphorylating many downstream targets such as P53 that are critical for radical detoxification, control of repair systems and control of cell cycle progression.

We are particularly interested in modeling DNA damage response pathway initiated by ATM activation. This model includes activation of ATM by DSBs, and the regulatory effects by ATM regulator PP2A, MRN complex (Bakkenist 2003, Goodarzi et al, 2004, Uziel et al.,2003)(Fig 1). We performed Hill function parameter fitting to experimental data (Goodarzi et al, 2004) to constrain the steady state, and compared our more detailed dynamical model with Chickarmane's ATM switch model (Chickarmane et al., 2005).

We also developed parameter optimization modules that enable us to estimate kinetic parameters of a nonlinear biochemical dynamical model from time-series metabolite concentration profiles. Parameter estimation here is defined as finding sets of model parameters that optimize an objective function that measures the goodness of fit between the model and experiment data.

Model

```
- theCascadeATMMRNPP2A = {  
  {ATM + ATM ⇌ ATMd, β1, δ1},  
  {ATM + ATMact ⇌ ATMhd, β2, δ2},  
  {ATMact → ATM, 0},  
  {ATMd → ATMhd, α1},  
  {ATMd ⇌MRNATMhd, a1, b1, c1, 0},  
  {ATMhd ⇌PP2AATMd, kf1, kr1, kcat1, 0},  
  {ATMhd → ATMact + ATMact, α2}  
}
```

Out[9] =

```
{ {2 ATM ⇌ ATMd, β1, δ1}, {ATM + ATMact ⇌ ATMhd, β2, δ2}, {ATMact → ATM, 0}, {ATMd → ATMhd, α1},  
  {ATMd ⇌MRNATMhd, a1, b1, c1, 0}, {ATMhd ⇌PP2AATMd, kf1, kr1, kcat1, 0}, {ATMhd → 2 ATMact, α2} }
```

Interpret the reaction and display ODE equations

```
- ODEs = interpret[theCascadeATMMRNPP2A, debug → False];
```

```
- TableForm[ODEs[[1]]]
```

Out[8]/TableForm =

```
ATM'[t] == -2 β1 ATM[t]2 + 0 ATMact[t] - β2 ATM[t] ATMact[t] + 2 δ1 ATMd[t] + δ2 ATMhd[t]  
ATMact'[t] == -0 ATMact[t] - β2 ATM[t] ATMact[t] + 2 α2 ATMhd[t] + δ2 ATMhd[t]  
ATMd'[t] == β1 ATM[t]2 - α1 ATMd[t] - δ1 ATMd[t] + b1 ATMd_MRN[t] + kcat1 ATMhd_PP2A[t] - a1 ATMd[t] MRN[t]  
ATMd_MRN'[t] == -b1 ATMd_MRN[t] - c1 ATMd_MRN[t] + a1 ATMd[t] MRN[t]  
ATMhd'[t] == β2 ATM[t] ATMact[t] + α1 ATMd[t] + c1 ATMd_MRN[t] - α2 ATMhd[t] - δ2 ATMhd[t] + kr1 ATMhd_PP2A[t] - kf1 ATMhd[t] PP2A[t]  
ATMhd_PP2A'[t] == -kcat1 ATMhd_PP2A[t] - kr1 ATMhd_PP2A[t] + kf1 ATMhd[t] PP2A[t]  
MRN'[t] == b1 ATMd_MRN[t] + c1 ATMd_MRN[t] - a1 ATMd[t] MRN[t]  
PP2A'[t] == kcat1 ATMhd_PP2A[t] + kr1 ATMhd_PP2A[t] - kf1 ATMhd[t] PP2A[t]
```

Fig 1: Cellerator model and ODEs for ATM activation and regulation module

Our parameter optimizer is a standalone program composed of a simulated annealing optimizer using Lam-Delosme schedule. The parameter optimizer brings in a biological model, experimental data, and algorithm parameter, generates a set of optimized values for model parameters. It runs on Linux/Unix environment. Multiple optimization tasks can be submitted and run in parallel on duo-core Linux cluster nodes (Xeon) via SGE. We evaluated the performance of our simulated annealing optimization algorithm in terms of fitness of the trajectory, fitness of parameters (parameter error) between models and experiments, final energy and computation time. We also studied the effect of algorithm parameters adjustment on the optimizer's performance.

Reference

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Christopher Bakkenist, Michael Kastan. DNA damage activates ATM through intermolecular autophosphorylation and dimmer dissociation. Nature. Vol 421: 499-506, 2003

Tamar Uziel, Yaniv Lerenthal, et al., Requirement of the MRN complex for ATM activation by DNA damage. The EMBO Journal vol 22, 5612-5621.2003

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