MAPK Cascade

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**Table 2. Predicted Hill coefficients for MAP kinase cascade components. Varying the assumed $K_m$ values**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Range of assumed $K_m$ values</th>
<th>MAPKK</th>
<th>MAPKK*</th>
<th>MAPK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MAPKKE $\rightarrow$ MAPKK</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.7</td>
<td>4.9</td>
</tr>
<tr>
<td>2. MAPKK $\rightarrow$ MAPKK*</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.7</td>
<td>4.9</td>
</tr>
<tr>
<td>3. MAPK $\rightarrow$ MAPKK-P</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.3-2.3</td>
<td>4.0-5.1</td>
</tr>
<tr>
<td>4. MAPKK-P $\rightarrow$ MAPKK</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.5-1.9</td>
<td>3.6-6.7</td>
</tr>
<tr>
<td>5. MAPKK-P $\rightarrow$ MAPKK-P</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.3-2.4</td>
<td>3.8-5.2</td>
</tr>
<tr>
<td>6. MAPKK-P-P $\rightarrow$ MAPKK-P</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.7-1.8</td>
<td>4.1-6.4</td>
</tr>
<tr>
<td>7. MAPK $\rightarrow$ MAPKK-P</td>
<td>60-1500 nM (300 nM^3)</td>
<td>1.0</td>
<td>1.7</td>
<td>3.7-6.2</td>
</tr>
<tr>
<td>8. MAPKK $\rightarrow$ MAPK</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.7</td>
<td>4.3-5.2</td>
</tr>
<tr>
<td>9. MAPK-P $\rightarrow$ MAPKK-P</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.7</td>
<td>3.4-6.1</td>
</tr>
<tr>
<td>10. MAPKK-P $\rightarrow$ MAPKK-P</td>
<td>60-1500 nM</td>
<td>1.0</td>
<td>1.7</td>
<td>4.7-5.1</td>
</tr>
</tbody>
</table>

The assumed $K_m$ values for each reaction were individually varied over the ranges shown, with the assumed $K_m$ values for the other nine reactions held constant. The effective Hill coefficients were calculated from the steepness of the predicted stimulus/response curves, as described in the text.

*The $K_m$ value for reaction 7 has been measured to be 300 nM for the phosphorylation of a mammalian MAPK by a MAPKK (N. Ahn, personal communication). All of the other $K_m$ values were initially assumed to be 300 nM as well.

**Calculations.** Eqs. 1-10 represent the reactions of the MAPK cascade, which are shown schematically in Fig. 1. We have used Goldbeter and Koshland's nomenclature for the rate constants—the letter a denotes association; d denotes dissociation without catalysis, and t denotes product formation (11). KKK denotes MAPKK; KK denotes MAPKK and K denotes MAPK.

1. KKK + E1 $\rightarrow$ KKK-E1 $\rightarrow$ KKK$^*$ + E1  
2. KKK$^*$ + E2 $\rightarrow$ KKK-E2 $\rightarrow$ KKK + E2  
3. KK + KKK$^*$ $\rightarrow$ KK+KKK$^*$  
4. KK-P + KPase $\rightarrow$ KK-P-KPase  
5. KK-P + KK$^*$ $\rightarrow$ KK+KK$^*$  
6. KKK-P + K + KPase $\rightarrow$ KKK-P+KP  
7. KKK-P + K $\rightarrow$ KKK-P-KP $\rightarrow$ KKK-P + P  
8. KKK-P + KPase $\rightarrow$ KKK-P-KPase $\rightarrow$ KKK-P + P  
9. KKK-P + PP $\rightarrow$ KKK-P-KP $\rightarrow$ KKK-P + PP  
10. KKK-P + PP $\rightarrow$ KKK-P-KPase $\rightarrow$ KKK-P + PP

Fig. 1. Schematic view of the MAPK cascade. Activation of MAPK depends upon the phosphorylation of two conserved sites [Thr-183 and Tyr-185 in rat p42 MAPK/Erk2 (4, 5)]. Full activation of MAPK requires phosphorylation of two sites [Ser-218 and Ser-222 in mouse Mek-1/MKK1 (6–10)]. Detailed mechanisms for the activation of various MAPKKs (e.g., Raf-1, B-Raf, Mos) are not yet established; here we assume that MAPKKs are activated and inactivated by enzymes we denote E1 and E2. MAPKK$^*$ denotes activated MAPKK. MAPKK-P and MAPKK-PP denote singly and doubly phosphorylated MAPKK, respectively. MAPK-P and MAPK-PP denote singly and doubly phosphorylated MAPK. Pase denotes phosphatase.
As 18 Ordinary Differential Equations
Plus 7 conservation equations

The 10 reactions described above give rise to 18 rate equations.

One equation for each species (8) and complex (10), but not for constant concentration enzymes (4)

In addition, there are seven conservation equations (Eqs. 29-35).

\[ [\text{KKK}]_{\text{tot}} = [\text{KKK}] + [\text{KKK}^*] + [\text{KKK} \cdot E1] + [\text{KKK} \cdot E2] \]

\[ + [\text{KKK}^* \cdot K] + [\text{KKK}^* \cdot K-P] \]

in exactly one state

Each molecule
The Circuit

E1

KKK → KKK*

KKK* → KK

KK → KK-P

KK-P → KK-PP

KK-PP → K

K → K-P

K-P → K-PP

K-PP

(input)

(output)
Enzymatic Reactions

Reaction View

\[ S \xrightarrow{(c,d,e)} E \xrightarrow{c} E+S \xrightarrow{e} P+E \]

Intermediate complex

Interaction View

\[ S() \triangleq \text{new } u@d \text{ new } k@e \]
\[ !a_c(u,k); (!u_d; S() + !k_e; P()) \]

Private bindings between one \( S \) and one \( E \) molecule

\[ E() \triangleq ?a_c(u,k); (?u_d; E() + ?k_e; E()) \]

\[ P() \triangleq ... \]
MAPK Cascade in SPiM

let KKK() =
  (new u1@d1:Release new k1@r1:React
   !a1(u1,k1); (do !u1;KKK() or !k1;KKKst()))
and KKKst() =
  (new u2@d2:Release new k2@r2:React
   do !a2(u2,k2); (do !u2;KKKst() or !k2;KKK())
   or ?a3(u3,k3); (do ?u3;KKKst() or ?k3;KKKst())
   or ?a5(u5,k5); (do ?u5;KKKst() or ?k5;KKKst())))

let E1() =
  ?a1(u1,k1); (do ?u1;E1() or ?k1;E1())

let E2() =
  ?a2(u2,k2); (do ?u2;E2() or ?k2;E2())

let KK() =
  (new u3@d3:Release new k3@r3:React
   !a3(u3,k3); (do !u3;KK() or !k3;KK_P())))
and KK_P() =
  (new u4@d4:Release new k4@r4:React
   do !a4(u4,k4); (do !u4;KK_P() or !k4;KK_P())
   or !a5(u5,k5); (do !u5;KK_P() or !k5;KK_PP())))

and KKPse() =
  do ?a4(u4,k4); (do ?u4;KKPse() or ?k4;KKPse())
  or ?a6(u6,k6); (do ?u6;KKPse() or ?k6;KKPse())

let K() =
  (new u7@d7:Release new k7@r7:React
   !a7(u7,k7); (do !u7;K() or !k7;K_P())))
and K_P() =
  (new u8@d8:Release new k8@r8:React
   new u9@d9:Release new k9@r9:React
   do !a8(u8,k8); (do !u8;K_P() or !k8;K())
   or !a9(u9,k9); (do !u9;K_P() or !k9;K_PP())))

and KPse() =
  do ?a8(u8,k8); (do ?u8;KPse() or ?k8;KPse())
  or ?a10(u10,k10); (do ?u10;KPse() or ?k10;KPse())

One process for each component (12) including enzymes, but not for complexes.

No need for conservation equations: implicit in “choice” operator in the calculus.
type Release = chan()

type React = chan()

type Bond = chan(Release, React)

new a1@1.0: Bond val d1=1.0 val r1=1.0
new a2@1.0: Bond val d2=1.0 val r2=1.0
new a3@1.0: Bond val d3=1.0 val r3=1.0
new a4@1.0: Bond val d4=1.0 val r4=1.0
new a5@1.0: Bond val d5=1.0 val r5=1.0
new a6@1.0: Bond val d6=1.0 val r6=1.0
new a7@1.0: Bond val d7=1.0 val r7=1.0
new a8@1.0: Bond val d8=1.0 val r8=1.0
new a9@1.0: Bond val d9=1.0 val r9=1.0
new a10@1.0: Bond val d10=1.0 val r10=1.0

...  

run 100 of KKK() run 100 of KK() run 100 of K()
run 1 of E2() run 1 of KKPse() run 1 of KPse()
run 1 of E1()
MAPK Cascade Simulation in SPiM

1st stage:
KKK* barely rises

2nd stage:
KK-PP rises, but is not stable

3rd stage:
K-PP flips up to max even anticipating 2nd stage

All coefficients 1.0!!!
100xKKK, 100xKK, 100xK,
5xE2, 5xKKPse, 5xKPse.

Input is 1xE1.
Output is 90xK-PP (ultrasensitivity).
**MAPK Cascade Simulation in SPiM**

All coefficients 1.0 !!!
100xKKK, 100xKK, 100xK,
13xE2, 13xKKPse, 13xKPse.
nxE1 as indicated
(1xE1 is not sufficient to produce an output)
MAPK Cascade Simulation in SPiM

Rates and concentrations from paper:

1xE2 (0.3 nM)
1xKKPase (0.3 nM)
120xKPase (120 nM)
3xKKK (3 nM)
1200xKK (1.2 uM)
1200xK (1.2 uM)

dx = rx = 150, ax = 1
(Km = (dx + rx) / ax, Km = 300 nM)

1xE1 injected