SI Appendix

Master Equations

The corresponding evolution of the probabilities of the states for the MAPK signal transduction pathway obey the master equations as follows:

$$
\begin{aligned}
X_1 &= KKK \\
X_2 &= E1 \\
X_3 &= KKK \cdot E1 \\
X_4 &= KKK^* \\
X_5 &= E2 \\
X_6 &= KKK \cdot E2 \\
X_7 &= KK \\
X_8 &= KK \cdot KKK \\
X_9 &= KK - P \\
\langle x_{10} \rangle &= KKP'ase \\
\langle x_{11} \rangle &= KK - P \cdot KKP'ase \\
\langle x_{12} \rangle &= KK - P \cdot KKK^* \\
\langle x_{13} \rangle &= KK - PP \\
\langle x_{14} \rangle &= KK - PP \cdot KKP'ase \\
\langle x_{15} \rangle &= K \\
\langle x_{16} \rangle &= KK - PP \cdot K \\
\langle x_{17} \rangle &= K - P \\
\langle x_{18} \rangle &= KP'ase \\
\langle x_{19} \rangle &= K - P \cdot KP'ase \\
\langle x_{20} \rangle &= K - P \cdot KK - PP \\
\langle x_{21} \rangle &= K - PP \\
\langle x_{22} \rangle &= KK - PP \cdot KP'ase
\end{aligned}
$$

Here $X_1, ...X_{22}$ represent 22 different protein enzymes illustrated above.

$\frac{\partial P}{\partial t} =$
$a1[(X_1+1)(X_2+1)P(X_1+1, X_2+1, X_3-1, ...) - X_1X_2P]+$
$a2[(X_4+1)(X_5+1)P(..., X_4+1, X_5+1, X_6-1, ...) - X_4X_5P]+$
$a3[(X_4+1)(X_7+1)P(..., X_4+1, ...X_7+1, X_8-1, ...) - X_4X_7P]+$
$a4[(X_9+1)(\langle x_{10}\rangle+1)P(..., X_9+1, \langle x_{10}\rangle+1, \langle x_{11}\rangle-1, ...) - X_9\langle x_{10}\rangle P]+$
$a5[(X_4+1)(X_9+1)P(..., X_4+1, ..., X_9+1, ..., \langle x_{12}\rangle-1, ...) - X_4X_9P]+$
$a6[(\langle x_{10}\rangle+1)(\langle x_{13}\rangle+1)P(..., \langle x_{10}\rangle+1, ..., \langle x_{13}\rangle+1, \langle x_{14}\rangle-1, ...) - \langle x_{10}\rangle\langle x_{13}\rangle P]+$
$a7[(\langle x_{13}\rangle+1)(\langle x_{15}\rangle+1)P(..., \langle x_{13}\rangle+1, ..., \langle x_{15}\rangle+1, \langle x_{16}\rangle-1, ...) - \langle x_{13}\rangle\langle x_{15}\rangle P]+$
$a8[(\langle x_{17}\rangle+1)(\langle x_{18}\rangle+1)P(..., \langle x_{17}\rangle+1, \langle x_{18}\rangle+1, \langle x_{19}\rangle-1, ...) - \langle x_{17}\rangle\langle x_{18}\rangle P]+$
$a9[(\langle x_{13}\rangle+1)(\langle x_{17}\rangle+1)P(..., \langle x_{13}\rangle+1, ..., \langle x_{17}\rangle+1, ..., \langle x_{20}\rangle-1, ...) - \langle x_{13}\rangle\langle x_{17}\rangle P]+$
$a10[(\langle x_{18}\rangle+1)(\langle x_{21}\rangle+1)P(..., \langle x_{18}\rangle+1, ..., \langle x_{21}\rangle+1, \langle x_{22}\rangle-1, ...) - \langle x_{18}\rangle\langle x_{21}\rangle P]+$
$d1[X_3P(X_1-1, X_2-1, X_3+1, ...) - X_3P]+$
$d2[X_6P(..., X_4-1, X_5-1, X_6+1, ...) - X_6P]+$
$d3[X_8P(..., X_4-1, ..., X_7-1, X_8+1, ...) - X_8P]+$
$d4[\langle x_{11}\rangle P(..., X_9-1, \langle x_{10}\rangle-1, \langle x_{11}\rangle+1, ...) - \langle x_{11}\rangle P]+$
$d5[\langle x_{12}\rangle P(..., X_4-1, ..., X_9-1, ..., \langle x_{12}\rangle+1, ...) - \langle x_{12}\rangle P]+$
$d6[\langle x_{14}\rangle P(..., \langle x_{10}\rangle-1, ..., \langle x_{13}\rangle-1, \langle x_{14}\rangle+1, ...) - \langle x_{14}\rangle P]+$
$d7[\langle x_{16}\rangle P(..., \langle x_{13}\rangle-1, ..., \langle x_{15}\rangle-1, \langle x_{16}\rangle+1, ...) - \langle x_{16}\rangle P]+$
$d8[\langle x_{19}\rangle P(..., \langle x_{17}\rangle-1, \langle x_{18}\rangle-1, \langle x_{19}\rangle+1, ...) - \langle x_{19}\rangle P]+$
$d9[\langle x_{20}\rangle P(..., \langle x_{13}\rangle-1, ..., \langle x_{17}\rangle-1, ..., \langle x_{20}\rangle+1, ...) - \langle x_{20}\rangle P]+$
$d10[\langle x_{22}\rangle P(..., \langle x_{18}\rangle-1, ..., \langle x_{21}\rangle-1, ..., \langle x_{22}\rangle+1, ...) - \langle x_{22}\rangle P]+$
$k1[X_3P(.., X_2-1, X_3+1, X_4-1, ...) - X_3P]+$
$k2[X_6P(X_1-1, X_5-1, X_6+1, ...) - X_6P]+$
$k3[X_8P(.., X_4-1, ..., X_8+1, X_9-1, ...) - X_8P]+$
$k4[\langle x_{11}\rangle P(.., X_7-1, ..., \langle x_{10}\rangle-1, \langle x_{11}\rangle+1, ...) - \langle x_{11}\rangle P]+$
$k5[\langle x_{12}\rangle P(.., X_4-1, ..., \langle x_{12}\rangle+1, \langle x_{13}\rangle-1, ...) - \langle x_{12}\rangle P]+$
$k6[\langle x_{14}\rangle P(.., X_9-1, \langle x_{10}\rangle-1, ..., \langle x_{14}\rangle+1, ...) - \langle x_{14}\rangle P]+$
$k7[\langle x_{16}\rangle P(.., \langle x_{13}\rangle-1, ..., \langle x_{16}\rangle+1, \langle x_{17}\rangle-1, ...) - \langle x_{16}\rangle P]+$
$k8[\langle x_{19}\rangle P(.., \langle x_{15}\rangle-1, ..., \langle x_{18}\rangle-1, \langle x_{19}\rangle+1, ...) - \langle x_{19}\rangle P]+$
$k9[\langle x_{20}\rangle P(.., \langle x_{13}\rangle-1, ..., \langle x_{20}\rangle+1, \langle x_{21}\rangle-1, ...) - \langle x_{20}\rangle P]+$
$k10[\langle x_{22}\rangle P(.., \langle x_{17}\rangle-1, \langle x_{18}\rangle-1, ..., \langle x_{22}\rangle+1, ...) - \langle x_{22}\rangle P]$

Self Consistent Mean Field Approximations

This master equation is still very difficult if there are many different types of particles, since the number of equations of this form will grow as $n_1 \times n_2 \times n_3 \times \ldots$. We will be making a self consistent mean field approximation [1, 2, 3, 4], that is $P(x_i, x_j, \ldots) = \prod_i P_i(x_i)$. This reduces the number of equations to $n_1 + n_2 + \ldots$.

Because the individual probability distributions are now independent, we can describe each $P_i(x_i)$ by a series of moments: $\langle x_i \rangle, \langle x_i^2 \rangle, \ldots, \langle x_i^n \rangle, \ldots$. Thus we can convert from a series of differential equations describing the probability to a series of moment differential equations. For example, we can calculate the first moment to infer the approximate Poisson distribution, we can calculate the second moment to infer the approximate Gaussian distribution for individual probability $P(X_i)$. The moment equations are listed below up to second order. We notice these moment equations are themselves closed (they don't depend on higher order moments) for MAPK, so they can be solved exactly. We did so numerically up to second order moment to infer the underlying distribution.

As mentioned above, the motivation of our self consistent method of split-

ting the variables is to reduce the dimensionality of the real networks from exponential number of degrees of freedom to polynomial number of degrees of freedom (from M^N to $M \times N$, here M is the number of specific proteins and N is the number of protein types.). We believe our approximation of splitting the variables is a reasonable one because our method is not a simple splitting of variables as an independent product but with a mean field type of approximation. In other words, even though the form of our probability is a product like $P(x_1, ..., x_p, ..., x_N) = P(x_1)...P(x_q)...P(x_N)$, each of the component, for example $P(x_q)$ is not entirely independent with the others. The effect of the interactions of other components is taken into account by the mean field or average of others on this particular component. So in order to solve each individual $P(x_q)$, a self consistent equation for $P(x_q)$ has to be solved taken into account of the mean field effects from averaging the other components. In other words, the interactions among different components is taken into account approximately by the self consistent way of solving the each component $P(x_q)$ in the back ground of the average effects of others. The self consistent method has been applied to multi-electron atom and multi atom molecule studies [5]. The results are usually in reasonable agreements with experiments. We believe that the self consistent method of splitting

may have a wide range of applicability from weak to medium interactions among the components of the networks. For strongly interacting networks, some other approximation scheme has to be developed to deal with the issue.

When we compare the interaction strengths of the components among themselves (diagonal or near diagonal) and with others (off-diagonal) through the rate coefficients in the correct units, we realize that the diagonal part (150) is about 50 times higher in rates than the off diagonal ones (3.17) (see the rate parameter table in this supplementary material). This implies that the interactions of the components with others are relatively weak compared with the individual components themselves. This would validate our self consistent mean field splitting approximations for weak interactions. We picked up a pair of components of MAPK networks. We solve the problem exactly for the pair through kinetic Monte Carlo method [6] without any approximations of splitting the variables and then collect the histograms to obtain the exact probability. We compare the exact results with our self consistent splitting method. We reach good agreements of the self consistent mean field splitting results with the exact results. The relative error is around 0.64%. We show the comparison results of the distribution in terms of the two components with the self consistent mean field splitting and exact method

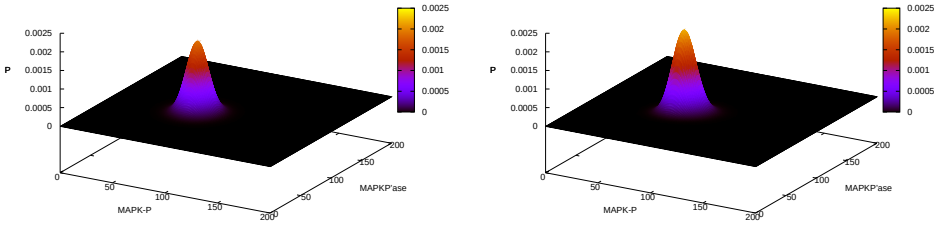

Figure 1: Comparison of the steady state probability distribution in terms of protein concentrations $K-P$ (variable 17) and $KP'ase$ (variable 18). A: Self consistent mean field results. B: Exact results.

in the figure.

The relative error is defined as: $\sigma = \sqrt{\frac{\sum_{ij}(P_{ij}^{exact} - P_{ij}^{self-consistent-mean-field})^2}{(\sum_{ij} P_{ij})^2}}$.

Non-Equilibrium Networks, Landscape, Flux and Entropy Production

For non-equilibrium system, the behavior is not entirely determined by the energy landscape alone even in the steady state. In fact the other crucial quantity not present in the equilibrium is the flux due to the fact that detailed balance is not guaranteed. We need both the landscape and flux to specify the behavior. Therefore, the dynamical trajectories in the non-equilibrium case are determined not only by the landscape as in the equilibrium case but also in addition by the flux (due to the lack of detailed balance). The landscape gradient and flux may not share the same direction. Therefore the trajectories can be very different from the ones guided only by the land-

scape alone. In analogy with the electrons moving in electric and magnetic field, the actual trajectories of the non-equilibrium systems are like spirals (instead of directly following the gradient of the potential) descending along the landscape gradient.

The entropy production rate we have calculated are the ones from the whole chemical reaction network. As mentioned we take into account the fact that the dynamic flow is determined by both the landscape and the flux. This will lead to the chemical potential and the current flux for the system in analogy to the electric circuit of electric voltages and currents. An electric circuit will dissipate energy, and the dissipation can be calculated when knowing the currents and voltages. The same thing applies here for the network. Once the chemical potential and current are known, we can calculate the dissipation via entropy production rate of the whole system.

From our calculations involving a pair of components, we have shown that the probability using our self consistent mean field splitting is close to the exact solution. The entropy production rate for the system is a sum of the various combinations of the probabilities and underlying chemical reaction rates ($\dot{S} = \sum_{ij} T_{ji} P_j ln(\frac{T_{ji} P_j}{T_{ij} P_i})$). Therefore, the entropy is a function of probability and underlying rates. Since the probabilities from the self consistent

mean field splitting method are close to the ones from exact method, the entropy production rate from the mean field splitting method are also quite close to the exact method.

For macro systems, the entropy production rate is only minimum for linear case. When we study here the MAPK network, we look at the probabilistic description taking into account the intrinsic fluctuations due to the finite number of molecules. In other words, even though the macroscopic MAPK system is nonlinear (in concentrations) in the form of the normal chemical rate equations of the average concentrations, the corresponding probabilistic descriptions following the Makovian master equations are linear (in the probability). The entropy production rate for this linear description of the probability is global and can be shown to be never decreasing [7, 8, 9]. We believe this is the reason why the entropy production is minimum and the definite of the entropy production is useful here.

Rate Parameters

The values used for the unperturbed rates, as determined by the Ferrel Lab, are in table 1. The values for the traditional reaction rate equations are in the first column. These has to be modified to work in the Master's equations by multiplying the a's by AV, where A is Avagadro's number and V is the

Table 1: Unperturbed reaction rates.

Variable	Reaction Rate Equations	Master's Equation
a_i	1000	3.171
d_i	150	150
k_i	150	150

volume of interest. $A = 6.022 \times 10^{23}$ and V can be taken for example as $V = 4/3 \times \pi \times (5 \times 10^{-6})^3\ m^3$.

Moment Equations

The first moment equations are:

$$\frac{d\langle x_1\rangle}{dt} = a_1\langle x_1\rangle\langle x_2\rangle - d_1\langle x_3\rangle - k_1\langle x_3\rangle$$
$$\frac{d\langle x_2\rangle}{dt} = -a_1\langle x_1\rangle\langle x_2\rangle + d_1\langle x_3\rangle + k_1\langle x_3\rangle$$
$$\frac{d\langle x_3\rangle}{dt} = a_2\langle x_4\rangle\langle x_5\rangle - d_2\langle x_6\rangle - k_2\langle x_6\rangle$$
$$\frac{d\langle x_4\rangle}{dt} = -a_1\langle x_1\rangle\langle x_2\rangle + d_1\langle x_3\rangle + k_2\langle x_6\rangle$$
$$\frac{d\langle x_5\rangle}{dt} = -a_2\langle x_4\rangle\langle x_5\rangle + d_2\langle x_6\rangle + k_2\langle x_6\rangle$$
$$\frac{d\langle x_6\rangle}{dt} = a_3\langle x_4\rangle\langle x_7\rangle - d_3\langle x_8\rangle - k_3\langle x_8\rangle$$
$$\frac{d\langle x_7\rangle}{dt} = a_4\langle x_9\rangle\langle x_{10}\rangle - d_4\langle x_{11}\rangle - k_4\langle x_{11}\rangle$$
$$\frac{d\langle x_8\rangle}{dt} = -a_3\langle x_4\rangle\langle x_7\rangle + d_3\langle x_8\rangle + k_4\langle x_{11}\rangle$$
$$\frac{d\langle x_9\rangle}{dt} = a_5\langle x_4\rangle\langle x_9\rangle - d_5\langle x_{12}\rangle - k_5\langle x_{12}\rangle$$
$$\frac{d\langle x_{10}\rangle}{dt} = k_1\langle x_3\rangle - a_2\langle x_4\rangle\langle x_5\rangle + d_2\langle x_6\rangle - a_3\langle x_4\rangle\langle x_7\rangle + d_3\langle x_8\rangle + k_3\langle x_8\rangle - a_5\langle x_4\rangle\langle x_9\rangle$$
$$+d_5\langle x_{12}\rangle + k_5\langle x_{12}\rangle$$
$$\frac{d\langle x_{11}\rangle}{dt} = a_6\langle x_{10}\rangle\langle x_{13}\rangle - d_6\langle x_{14}\rangle - k_6\langle x_{14}\rangle$$
$$\frac{d\langle x_{12}\rangle}{dt} = k_3\langle x_8\rangle - a_5\langle x_4\rangle\langle x_9\rangle - a_4\langle x_9\rangle\langle x_{10}\rangle + d_4\langle x_{11}\rangle + d_5\langle x_{12}\rangle + k_6\langle x_{14}\rangle$$
$$\frac{d\langle x_{13}\rangle}{dt} = -a_4\langle x_9\rangle\langle x_{10}\rangle + d_4\langle x_{11}\rangle + k_4\langle x_{11}\rangle - a_6\langle x_{10}\rangle\langle x_{13}\rangle + d_6\langle x_{14}\rangle + k_6\langle x_{14}\rangle$$
$$\frac{d\langle x_{14}\rangle}{dt} = a_7\langle x_{13}\rangle\langle x_{15}\rangle - d_7\langle x_{16}\rangle - k_7\langle x_{16}\rangle$$
$$\frac{d\langle x_{15}\rangle}{dt} = a_8\langle x_{17}\rangle\langle x_{18}\rangle - d_8\langle x_{19}\rangle - k_8\langle x_{19}\rangle$$
$$\frac{d\langle x_{16}\rangle}{dt} = -a_7\langle x_{13}\rangle\langle x_{15}\rangle + d_7\langle x_{16}\rangle + k_8\langle x_{19}\rangle$$
$$\frac{d\langle x_{17}\rangle}{dt} = a_9\langle x_{13}\rangle\langle x_{17}\rangle - d_9\langle x_{20}\rangle - k_9\langle x_{20}\rangle$$
$$\frac{d\langle x_{18}\rangle}{dt} = k_5\langle x_{12}\rangle - a_6\langle x_{10}\rangle\langle x_{13}\rangle + d_6\langle x_{14}\rangle - a_7\langle x_{13}\rangle\langle x_{15}\rangle + d_7\langle x_{16}\rangle + k_7\langle x_{16}\rangle - a_9\langle x_{13}\rangle\langle x_{17}\rangle$$
$$+d_9\langle x_{20}\rangle + k_9\langle x_{20}\rangle$$
$$\frac{d\langle x_{19}\rangle}{dt} = k_9\langle x_{20}\rangle - a_{10}\langle x_{18}\rangle\langle x_{21}\rangle + d_{10}\langle x_{22}\rangle$$
$$\frac{d\langle x_{20}\rangle}{dt} = a_{10}\langle x_{18}\rangle\langle x_{21}\rangle - d_{10}\langle x_{22}\rangle - k_{10}\langle x_{22}\rangle$$
$$\frac{d\langle x_{21}\rangle}{dt} = k_7\langle x_{16}\rangle - a_9\langle x_{13}\rangle\langle x_{17}\rangle - a_8\langle x_{17}\rangle\langle x_{18}\rangle + d_8\langle x_{19}\rangle + d_9\langle x_{20}\rangle + k_{10}\langle x_{22}\rangle$$
$$\frac{d\langle x_{22}\rangle}{dt} = -a_8\langle x_{17}\rangle\langle x_{18}\rangle + d_8\langle x_{19}\rangle + k_8\langle x_{19}\rangle - a_{10}\langle x_{18}\rangle\langle x_{21}\rangle + d_{10}\langle x_{22}\rangle + k_{10}\langle x_{22}\rangle$$

The second order moment equations are as follows:

$$\frac{d\langle x_1^2\rangle}{dt} = -2a_1\langle x_1^2\rangle\langle x_2\rangle + a_1\langle x_1\rangle\langle x_2\rangle + d_1\langle x_3\rangle + 2d_1\langle x_1\rangle\langle x_3\rangle + k_2\langle x_6\rangle + 2k_2\langle x_1\rangle\langle x_6\rangle$$
$$\frac{d\langle x_2^2\rangle}{dt} = -2a_1\langle x_2^2\rangle\langle x_1\rangle + a_1\langle x_1\rangle\langle x_2\rangle + d_1\langle x_3\rangle + k_1\langle x_3\rangle + 2d_1\langle x_2\rangle\langle x_3\rangle + 2k_1\langle x_2\rangle\langle x_3\rangle$$
$$\frac{d\langle x_3^2\rangle}{dt} = -2d_1\langle x_3^2\rangle - 2k_1\langle x_3^2\rangle + a_1\langle x_1\rangle\langle x_2\rangle + d_1\langle x_3\rangle + k_1\langle x_3\rangle + 2a_1\langle x_1\rangle\langle x_2\rangle\langle x_3\rangle$$
$$\frac{d\langle x_4^2\rangle}{dt} = k_1\langle x_3\rangle + 2k_1\langle x_3\rangle\langle x_4\rangle - 2a_2\langle x_4^2\rangle\langle x_5\rangle + a_2\langle x_4\rangle\langle x_5\rangle + d_2\langle x_6\rangle + 2d_2\langle x_4\rangle\langle x_6\rangle$$
$$-2a_3\langle x_4^2\rangle\langle x_7\rangle$$
$$+a_3\langle x_4\rangle\langle x_7\rangle + d_3\langle x_8\rangle + k_3\langle x_8\rangle + 2d_3\langle x_4\rangle\langle x_8\rangle + 2k_3\langle x_4\rangle\langle x_8\rangle - 2a_5\langle x_4^2\rangle\langle x_9\rangle + a_5\langle x_4\rangle\langle x_9\rangle$$
$$+d_5\langle x_{12}\rangle$$
$$+k_5\langle x_{12}\rangle + 2d_5\langle x_4\rangle\langle x_{12}\rangle + 2k_5\langle x_4\rangle\langle x_{12}\rangle$$
$$\frac{d\langle x_5^2\rangle}{dt} = -2a_2\langle x_5^2\rangle\langle x_4\rangle + a_2\langle x_4\rangle\langle x_5\rangle + d_2\langle x_6\rangle + k_2\langle x_6\rangle + 2d_2\langle x_5\rangle\langle x_6\rangle + 2k_2\langle x_5\rangle\langle x_6\rangle$$
$$\frac{d\langle x_6^2\rangle}{dt} = -2d_2\langle x_6^2\rangle - 2k_2\langle x_6^2\rangle + a_2\langle x_4\rangle\langle x_5\rangle + d_2\langle x_6\rangle + k_2\langle x_6\rangle + 2a_2\langle x_4\rangle\langle x_5\rangle\langle x_6\rangle$$
$$\frac{d\langle x_7^2\rangle}{dt} = -2a_3\langle x_7^2\rangle\langle x_4\rangle + a_3\langle x_4\rangle\langle x_7\rangle + d_3\langle x_8\rangle + 2d_3\langle x_7\rangle\langle x_8\rangle + k_4\langle x_{11}\rangle + 2k_4\langle x_7\rangle\langle x_{11}\rangle$$
$$\frac{d\langle x_8^2\rangle}{dt} = -2d_3\langle x_8^2\rangle - 2k_3\langle x_8^2\rangle + a_3\langle x_4\rangle\langle x_7\rangle + d_3\langle x_8\rangle + k_3\langle x_8\rangle + 2a_3\langle x_4\rangle\langle x_7\rangle\langle x_8\rangle$$
$$\frac{d\langle x_9^2\rangle}{dt} = -2a_5\langle x_9^2\rangle\langle x_4\rangle + k_3\langle x_8\rangle + a_5\langle x_4\rangle\langle x_9\rangle + 2k_3\langle x_8\rangle\langle x_9\rangle - 2a_4\langle x_9^2\rangle\langle x_{10}\rangle + a_4\langle x_9\rangle\langle x_{10}\rangle$$
$$+d_4\langle x_{11}\rangle$$
$$+2d_4\langle x_9\rangle\langle x_{11}\rangle + d_5\langle x_{12}\rangle + 2d_5\langle x_9\rangle\langle x_{12}\rangle + k_6\langle x_{14}\rangle + 2k_6\langle x_9\rangle\langle x_{14}\rangle$$
$$\frac{d\langle x_{10}^2\rangle}{dt} = -2a_4\langle x_{10}^2\rangle\langle x_9\rangle + a_4\langle x_9\rangle\langle x_{10}\rangle + d_4\langle x_{11}\rangle + k_4\langle x_{11}\rangle + 2d_4\langle x_{10}\rangle\langle x_{11}\rangle + 2k_4\langle x_{10}\rangle\langle x_{11}\rangle$$
$$-2a_6\langle x_{10}^2\rangle\langle x_{13}\rangle + a_6\langle x_{10}\rangle\langle x_{13}\rangle + d_6\langle x_{14}\rangle + k_6\langle x_{14}\rangle + 2d_6\langle x_{10}\rangle\langle x_{14}\rangle + 2k_6\langle x_{10}\rangle\langle x_{14}\rangle$$
$$\frac{d\langle x_{11}^2\rangle}{dt} = -2d_4\langle x_{11}^2\rangle - 2k_4\langle x_{11}^2\rangle + a_4\langle x_9\rangle\langle x_{10}\rangle + d_4\langle x_{11}\rangle + k_4\langle x_{11}\rangle + 2a_4\langle x_9\rangle\langle x_{10}\rangle\langle x_{11}\rangle$$
$$\frac{d\langle x_{12}^2\rangle}{dt} = -2d_5\langle x_{12}^2\rangle - 2k_5\langle x_{12}^2\rangle + a_5\langle x_4\rangle\langle x_9\rangle + d_5\langle x_{12}\rangle + k_5\langle x_{12}\rangle + 2a_5\langle x_4\rangle\langle x_9\rangle\langle x_{12}\rangle$$
$$\frac{d\langle x_{13}^2\rangle}{dt} = -2a_6\langle x_{13}^2\rangle\langle x_{10}\rangle + k_5\langle x_{12}\rangle + a_6\langle x_{10}\rangle\langle x_{13}\rangle + 2k_5\langle x_{12}\rangle\langle x_{13}\rangle + d_6\langle x_{14}\rangle + 2d_6\langle x_{13}\rangle\langle x_{14}\rangle$$
$$-2a_7\langle x_{13}^2\rangle\langle x_{15}\rangle + a_7\langle x_{13}\rangle\langle x_{15}\rangle + d_7\langle x_{16}\rangle + k_7\langle x_{16}\rangle + 2d_7\langle x_{13}\rangle\langle x_{16}\rangle + 2k_7\langle x_{13}\rangle\langle x_{16}\rangle$$
$$-2a_9\langle x_{13}^2\rangle\langle x_{17}\rangle$$
$$+a_9\langle x_{13}\rangle\langle x_{17}\rangle + d_9\langle x_{20}\rangle + k_9\langle x_{20}\rangle + 2d_9\langle x_{13}\rangle\langle x_{20}\rangle + 2k_9\langle x_{13}\rangle\langle x_{20}\rangle$$
$$\frac{d\langle x_{14}^2\rangle}{dt} = -2d_6\langle x_{14}^2\rangle - 2k_6\langle x_{14}^2\rangle + a_6\langle x_{10}\rangle\langle x_{13}\rangle + d_6\langle x_{14}\rangle + k_6\langle x_{14}\rangle + 2a_6\langle x_{10}\rangle\langle x_{13}\rangle\langle x_{14}\rangle$$
$$\frac{d\langle x_{15}^2\rangle}{dt} = -2a_7\langle x_{15}^2\rangle\langle x_{13}\rangle + a_7\langle x_{13}\rangle\langle x_{15}\rangle + d_7\langle x_{16}\rangle + 2d_7\langle x_{15}\rangle\langle x_{16}\rangle + k_8\langle x_{19}\rangle + 2k_8\langle x_{15}\rangle\langle x_{19}\rangle$$
$$\frac{d\langle x_{16}^2\rangle}{dt} = -2d_7\langle x_{16}^2\rangle - 2k_7\langle x_{16}^2\rangle + a_7\langle x_{13}\rangle\langle x_{15}\rangle + d_7\langle x_{16}\rangle + k_7\langle x_{16}\rangle + 2a_7\langle x_{13}\rangle\langle x_{15}\rangle\langle x_{16}\rangle$$
$$\frac{d\langle x_{17}^2\rangle}{dt} = -2a_9\langle x_{17}^2\rangle\langle x_{13}\rangle + k_7\langle x_{16}\rangle + a_9\langle x_{13}\rangle\langle x_{17}\rangle + 2k_7\langle x_{16}\rangle\langle x_{17}\rangle - 2a_8\langle x_{17}^2\rangle\langle x_{18}\rangle$$
$$+a_8\langle x_{17}\rangle\langle x_{18}\rangle + d_8\langle x_{19}\rangle + 2d_8\langle x_{17}\rangle\langle x_{19}\rangle + d_9\langle x_{20}\rangle + 2d_9\langle x_{17}\rangle\langle x_{20}\rangle + k_{10}\langle x_{22}\rangle + 2k_{10}\langle x_{17}\rangle\langle x_{22}\rangle$$
$$\frac{d\langle x_{18}^2\rangle}{dt} = -2a_8\langle x_{18}^2\rangle\langle x_{17}\rangle + a_8\langle x_{17}\rangle\langle x_{18}\rangle + d_8\langle x_{19}\rangle + k_8\langle x_{19}\rangle + 2d_8\langle x_{18}\rangle\langle x_{19}\rangle + 2k_8\langle x_{18}\rangle\langle x_{19}\rangle$$
$$-2a_{10}\langle x_{18}^2\rangle\langle x_{21}\rangle + a_{10}\langle x_{18}\rangle\langle x_{21}\rangle + d_{10}\langle x_{22}\rangle + k_{10}\langle x_{22}\rangle + 2d_{10}\langle x_{18}\rangle\langle x_{22}\rangle + 2k_{10}\langle x_{18}\rangle\langle x_{22}\rangle$$
$$\frac{d\langle x_{19}^2\rangle}{dt} = -2d_8\langle x_{19}^2\rangle - 2k_8\langle x_{19}^2\rangle + a_8\langle x_{17}\rangle\langle x_{18}\rangle + d_8\langle x_{19}\rangle + k_8\langle x_{19}\rangle + 2a_8\langle x_{17}\rangle\langle x_{18}\rangle\langle x_{19}\rangle$$
$$\frac{d\langle x_{20}^2\rangle}{dt} = -2d_9\langle x_{20}^2\rangle - 2k_9\langle x_{20}^2\rangle + a_9\langle x_{13}\rangle\langle x_{17}\rangle + d_9\langle x_{20}\rangle + k_9\langle x_{20}\rangle + 2a_9\langle x_{13}\rangle\langle x_{17}\rangle\langle x_{20}\rangle$$
$$\frac{d\langle x_{21}^2\rangle}{dt} = -2a_{10}\langle x_{21}^2\rangle\langle x_{18}\rangle + k_9\langle x_{20}\rangle + a_{10}\langle x_{18}\rangle\langle x_{21}\rangle + 2k_9\langle x_{20}\rangle\langle x_{21}\rangle + d_{10}\langle x_{22}\rangle$$
$$+2d_{10}\langle x_{21}\rangle\langle x_{22}\rangle$$
$$\frac{d\langle x_{22}^2\rangle}{dt} = -2d_{10}\langle x_{22}^2\rangle - 2k_{10}\langle x_{22}^2\rangle + a_{10}\langle x_{18}\rangle\langle x_{21}\rangle + d_{10}\langle x_{22}\rangle + k_{10}\langle x_{22}\rangle + 2a_{10}\langle x_{18}\rangle\langle x_{21}\rangle\langle x_{22}\rangle$$

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