Supporting Table S1 Summary of published mathematical models for miRNA effect on expression

miRNA model ref.	mRNA synthesis	miRNA synthesis	mRNA miRNA binding	Role of P-body	Translation by complex	Degradation of complex	Recovery of miRNA	Recovery of mRNA	Model Type	miRNA-mRNA number.
(Levine et al. 2007)	Unregulated	Unregulated	Reversible	By considering mRNA in the processed state	At the same rate as mRNA translation	At a rate more than that of mRNA	Not considered	Not considered	Deterministic	one-one
(Khanin and Higham 2007)	Unregulated	Unregulated	Reversible	Not considered	At a lower rate than mRNA translation	At a rate more than that of mRNA	Considered	Not considered	Deterministic	one-two
(Mitarai et al. 2007)	Unregulated	Regulated by protein	Irreversible	Not considered	Not considered	Second order kinetic	Not considered	Not considered	Deterministic	1-many
(Zhdanov 2008)	Unregulated	Regulated by protein	Irreversible	Not considered	Not considered	miRNA concentration dependent	Not considered	Not considered	Deterministic	1-many
(Zhdanov 2009)	Unregulated	Single step unregulated	Irreversible	Not considered	Not considered	Rate is limited by miRNA diffusion range from 10-4 to 10-2 min-1.	Not considered	Not considered	Deterministic &	1-100
(Vohradsky et al. 2010)	Unregulated	Unregulated	Irreversible (not explicitly considered)	Not considered	Not considered	miRNA concentration dependent saturating mRNA degradation	Not considered	Not considered	Deterministic	1-many

(Arvey et al. 2010)	Unregulated	Unregulated	Reversible	Not considered	Not considered	Not considered	Considered	Not considered	Deterministic	1-many
(Jia et al. 2009)	Unregulated	Unregulated	Not considered	Not considered	Not considered	Second order	Not considered	Not considered	Stochastic	one-two
(Mukherji et al. 2011)	Unregulated	Unregulated	Irreversible	Not considered	Not considered		Not-Considered	Not considered	Deterministic	1-1(multiple binding sites of similar mi) (many)
(Whichard et al. 2011)	Unregulated	Unregulated	Reversible	Not considered	Not considered	miRNA degradation must be smaller than a function of the kinetic parameters associated with the mRNA-miRNA complex	Not considered	Not considered	Deterministic	one-one
(Gokhale and Gadgil 2012)	Unregulated	Unregulated	Reversible	By considering the complex which can return either mRNA or miRNA	At a lower rate than mRNA translation	At a rate more than that of mRNA	Considered	Considered	Deterministic & Stochastic	one-one
(Figliuzzi et al. 2013)	Unregulated	Unregulated	Reversible	Not considered	Not considered	Depends on stoichiometry of complex	Considered	Not considered	Deterministic	Many-Many

(Ala et al. 2013)	Unregulated	Unregulated	Reversible	Not considered	Not considered	Measure of catalysis of miRNA on its target	Considered	Not considered	Deterministic	1-many
(Bosia et al. 2013)	Unregulated	Unregulated	Reversible	Not considered	Not considered	Considered as effective rate i.e (combined association, dissociation and degradation)	Considered	Not considered	Stochastic	Many-many
(Gérard and Novák 2013)	Unregulated	Unregulated	Reversible	Not considered	Not considered	Considered	Not considered	Not considered	Deterministic and Stochastic	Many-many
(Noorbakhsh et al. 2013)	Unregulated	Unregulated	Reversible	Not considered	Not considered	Considered	Not considered	Not considered	Stochastic	1-many

Supporting Information Section S.1

Generalized ordinary differential equations for M mRNA- NmiRNA(Non-Competitive Model)

We first consider the general case of a system of *M* mRNAs $m_i, i = 1,2,...,M$ interacting with *N* miRNAs μ_j, $j = 1,2,...,N$. Throughout, the same symbols are used in a context-dependent manner for entities and their concentrations. We model an open system with each m_i and μ_j being formed with a zero-order birth rate b_i^m and b_j^μ respectively. We assume that each mRNA m_i can bind to every miRNA μ_j with second order association rate constants k_{ij}^+. The resulting complexes c_{ij} can undergo first order dissociation (rate constant k_{ij}^-), stoichiometric degradation (rate constant d_{ij}^-), or selective degradation of either the miRNA (catalytic miRNA degradation with mRNA returned, rate constant k_{ij}^{retm}) or selective degradation of mRNA (catalytic mRNA degradation where miRNAis recycled, rate constant $k_{ij}^{ret\mu}$). If MREs on the mRNA are overlapping, only a single miRNA can bind to each mRNA, and 'combicomplexes' with multiple miRNA simultaneously bound to the same mRNA cannot exist. In such a competitive binding situation, miRNAs compete to bind to the mRNA. If MREs are non-overlapping, there is a possibility of combicomplex formation where free miRNAs bind to existing complexes. This can continue till an unrealistic complex $c_{i123..N}$ of one mRNA and all miRNA is formed. However, given practical considerations of the limited nucleotide real estate available on mRNA and site accessibility, we limit the analysis here to assume that at most two miRNAs can bind to a single mRNA to form a combicomplex $c_{ijj'}$ (*i=1,2,…M; j,j' =1,2,…,N; j<j'*). These combicomplexes are formed either by complex c_{ij} binding to miRNA j', with second order association rate $k_{ijj'}^+$, or by complex $c_{ij'}$ binding to μ_j with second order association rate $k_{ij'j}^+$. Each combicomplex $c_{ijj'}$ and complex c_{ij} containing mRNA m_i, as well as the unbound mRNA m_i can serve as a template for first-order formation of protein p_i with translation rate constants $b_{ijj'}^p$, b_{ij}^p and b_i^p respectively. Protein, mRNA, miRNA, and combicomplexes are assumed to undergo first order degradation with rate constants d_i^p, d_i^m, d_j^μ and $d_{ijj'}^c$ respectively. The differential equations for the non-competitive model are given below:

$\frac{d[m_i]}{dt} = b_i^m - d_i^m m_i - \sum_{j=1}^{N} k_{ij}^+ m_i \mu_j + \sum_{j=1}^{N} k_{ij}^- c_{ij} + \sum_{j=1}^{N} k_{ij}^{retm} c_{ij}$
$\frac{d[\mu_j]}{dt} = b_j^\mu - d_j^\mu \mu_j - \sum_{i=1}^{M} k_{ij}^+ m_i \mu_j + \sum_{i=1}^{M} k_{ij}^- c_{ij} + \sum_{i=1}^{M} \sum_{j'=1, j' \neq j}^{N} [k_{ij'j}^- c_{ijj'} - k_{ij'j}^+ c_{ij'} \mu_j] + \sum_{i=1}^{M} k_{ij}^{ret\mu} c_{ij}$

$\frac{d[c_{ij}]}{dt} = k_{ij}^{+} m_i \mu_j - k_{ij}^{-} c_{ij} + \sum_{j'=1, j' \neq j}^{N} [k_{ijj'}^{-} c_{ijj'} - k_{ijj'}^{+} c_{ij} \mu_{j'}] - k_{ij}^{retm} c_{ij} - k_{ij}^{ret\mu} c_{ij} - d_{ij}^{c} c_{ij}$
$\frac{d[c_{ijj'}]}{dt} = k_{ijj'}^{+} c_{ij} \mu_{j'} + k_{ij'j}^{+} c_{ij'} \mu_j - k_{ijj'}^{-} c_{ijj'} - k_{ij'j}^{-} c_{ijj'} - d_{ijj'}^{'} c_{ijj'}$
$\frac{d[p_i]}{dt} = b_i^p m_i - d_i^p [p_i] + \sum_{j=1}^{N} b_{ij}^p c_{ij} + \sum_{j, j'=1; j'>j}^{N} b_{ijj'}^p c_{ijj'}$

Section S.2

Steady state solution for the system in SI Section S.1

Since there is no feedback regulation of miRNA or mRNA by the protein products, and since complex phenomena such as enhancement of degradation upon translation are ignored, the reduction of the system of ordinary differential equations to nonlinear equations for derivation of the steady state concentrations is quite straightforward, and given below. Figluizzi et al(Figliuzzi et al. 2013c) consider a subset of this system that does not include combicomplex formation. Like the results obtained in that paper, we were unable to derive explicit expressions for the steady state RNA and protein concentrations as a function only of the reaction rate constants without linearization approximations. The reduced system of equations below may be used for symbolic or numerical computations for specific situations. At steady state the rate of change of species with respect to time is zero. Thus the above differential equations can be equated to zero and the steady state expressions for the generalised system are obtained.

$$c_{ijj'} = \frac{k^{+}_{ijj'} c_{ij} \mu_{j'} + k^{+}_{ij'j} c_{ij'} \mu_{j}}{k^{-}_{ijj'} + k^{-}_{ij'j} + d^{'}_{ijj'}}$$

$$p_i = \frac{b^{p}_{i}[m_i] + \sum_{j=1}^{N} b^{p}_{ij} c_{ij} + \sum_{j,j'=1;j'<j}^{N} b^{p}_{ijj'}[c_{ijj'}]}{d^{p}_{i}}$$

$$m_i = \frac{b^{m}_{i} + \sum_{j=1}^{N} (k^{-}_{ij} + k^{retm}_{ij}) c_{ij}}{d^{m}_{i} + \sum_{j=1}^{N} k^{+}_{ij} \mu_j}$$

$$0 = k^{+}_{ij} m_i \mu_j - k^{-}_{ij} c_{ij} + \sum_{j'=1, j' \neq j}^{N} [k^{-}_{ijj'} c_{ijj'} - k^{+}_{ijj'} c_{ij} \mu_{j'}] - k^{retm}_{ij} c_{ij} - k^{ret\mu}_{ij} c_{ij} - d^{c}_{ij} c_{ij}$$

$$0 = b^{\mu}_{j} - d^{\mu}_{j} \mu_j - \sum_{i=1}^{M} k^{+}_{ij} m_i \mu_j + \sum_{i=1}^{M} k^{-}_{ij} c_{ij} + \sum_{i=1}^{M} \sum_{j'=1, j' \neq j}^{N} [k^{-}_{ij'j} c_{ijj'} - k^{+}_{ij'j} c_{ij'} \mu_j] + \sum_{i=1}^{M} k^{ret\mu}_{ij} c_{ij}$$

Section S.3 Equation for 1mRNA-2miRNA at Steady State (Competitive Model)

$0 = b_1^m - d_1^m m_1 - k_{11}^+ m_1 \mu_1 - k_{12}^+ m_1 \mu_2 + k_{11}^- c_{11} + k_{12}^- c_{12} + k_{11}^{retm} c_{11} + k_{12}^{retm} c_{12}$
$0 = b_1^\mu - d_1^\mu \mu_1 - k_{11}^+ m_1 \mu_1 + k_{11}^- c_{11} + k_{11}^{ret\mu} c_{11}$
$0 = b_2^\mu - d_1^\mu \mu_2 - k_{12}^+ m_1 \mu_2 + k_{12}^- c_{12} + k_{12}^{ret\mu} c_{12}$
$0 = k_{11}^+ m_1 \mu_1 - k_{11}^- c_{11} - k_{11}^{retm} c_{11} - k_{11}^{ret\mu} c_{11} - d_{11}^c c_{11}$
$0 = k_{12}^+ m_1 \mu_2 - k_{12}^- c_{12} - k_{12}^{retm} c_{12} - k_{12}^{ret\mu} c_{12} - d_{12}^c c_{12}$
$0 = b_1^p m_1 - d_1^p p_1 + b_{11}^p c_{11} + b_{12}^p c_{12}$

Section S.4 Reduced System of equationsfor 1 mRNA-2 miRNA system (competitive model)–

The above system of non-linear algebraic equations was solved to obtain a reduced system of equations, where steady state levels of some of the components $m_1\mu_1, \mu_1, m_1, p_1$ can be expressed in terms reaction rate parameters and other components.

$$c_{11} = \frac{k_{11}^{+} m_1 \mu_1}{k_{11}^{-} + d_{11}^{c} + k_{11}^{retm} + k_{11}^{ret\mu}} \quad \text{(S.4.1)}$$

$$c_{12} = \frac{k_{12}^{+} m_1 \mu_2}{k_{12}^{-} + d_{12}^{c} + k_{12}^{retm} + k_{12}^{ret\mu}} \quad \text{(S.4.2)}$$

$$\mu_1 = \frac{b_1^{\mu}}{d_1^{\mu} + \frac{k_{11}^{+}(k_{11}^{retm} + d_{11}^{c})}{k_{11}^{retm} + k_{11}^{ret\mu} + d_{11}^{c} + k_{11}^{-}}[\mathrm{m}_1]} \quad \text{(S.4.3)}$$

$$\mu_2 = \frac{b_2^{\mu}}{d_2^{\mu} + \frac{k_{12}^{+}(k_{12}^{retm} + d_{12}^{c})}{k_{12}^{retm} + k_{12}^{ret\mu} + d_{12}^{c} + k_{12}^{-}}[\mathrm{m}_1]} \quad \text{(S.4.4)}$$

Free miRNA concentrations can be expressed solely as a function of free mRNA concentration. Substituting S.4.3 in S.4.1 and S.4.4 in S.4.2 in the first two equations leads to equations relating complex concentrations to the concentration of free mRNA. Substituting these in the equation below (S.4.5) leads to a nonlinear equation in one variable [m1] that can be numerically or analytically solved.

$$0 = b_1^{m} - d_1^{m} m_1 - k_{11}^{+} m_1 \mu_1 - k_{12}^{+} m_1 \mu_2 + k_{11}^{-} c_{11} + k_{12}^{-} c_{12} + k_{11}^{retm} c_{11} + k_{12}^{retm} c_{12} \quad \text{(S.4.5)}$$

Knowing free mRNA concentrations, the concentrations of the complexes can be calculated as a function of rate constants, and the protein concentration can be calculated using

$$p_1 = \frac{b_1^{p}[m_1] + b_{11}^{p} c_{11} + b_{12}^{p} c_{12}}{d_1^{p}}$$

This system was solved to obtain the expression for steady state level of components in terms of reaction rate parameters using Mathematica. The expression for steady state level of protein is available as Mathematica file SI File S2.

Section S.5 Steady state expressions for 1mRNA-1miRNA system

For a 1 mRNA-1 miRNA system, the differential equations are given by

$\frac{dm_1}{dt} = b_1^m - d_1^m m_1 - k_{11}^+ m_1 \mu_1 + k_{11}^- c_{11} + k_{11}^{retm} c_{11}$
$\frac{d\mu_1}{dt} = b_1^\mu - d_1^\mu \ \mu_1 - k_{11}^+ \ m_1 \ \mu_1 + k_{11}^- \ c_{11} + k_{11}^{ret\mu} c_{11}$
$\frac{dc_{11}}{dt} = k_{11}^+ m_1 \mu_1 - k_{11}^- c_{11} - k_{11}^{ret\mu} c_{11} - k_{11}^{retm} c_{11} - d_{11}^c c_{11}$
$\frac{dp_1}{dt} = b_1^p m_1 - d_1^p p_1 + b_{11}^p c_{11}$

At steady state, setting the all LHS to zero, we can solve for m_1, μ_1 and c_{11} and substitute these expressions in the steady state equation for the protein concentration given by

$p_1 = \frac{b_1^p m_1 + b_{11}^p c_{11}}{d_1^p}$. If there is no miRNA, the steady state protein level is given by $p_1 = \frac{b_1^p m_1}{d_1^p}$

Here, the steady state mRNA concentration is different as there is no modulation due to binding to miRNA. It is clear that if the effect of miRNA is to stabilize the transcript such that the total degradation constant is less than the degradation constant for unbound mRNA, or if the effect is to enhance translation ($b_1^p \ \leq \ b_{11}^p$) the steady state protein concentration will be greater with more bound complex, or in general will increase as the miRNA formation rate increases. In the simulations here, the parameters used are such that such effects are not possible. Here, the miRNA binding leads to degradation of the bound complex with a total (stoichiometric+nonstoichiometric) degradation rate that is not less than the degradation rate for unbound mRNA. We have also simulated a condition when the degradation rate of bound mRNA is 50% more than the unbound mRNA, and the results are qualitatively identical.

Upon solving the first three equations sequentially and then substituting the values for steady state m_1 and c_{11} in the equation for protein concentration, we can derive the steady state protein concentration in terms of the reaction network parameters as given below.

$$p = ((d_1^m)^2 d_1^\mu (d_{11}^c + k_{11}^- + k_{11}^{retm} + k_{11}^{ret\mu}) b_{11}^p + k_{11}^+ b_1^p (d_{11}^c + k_{11}^{ret\mu})(b_1^m (d_{11}^c + k_{11}^{retm}) - (d_{11}^c + k_{11}^{ret\mu}) b_1^\mu) + d_1^m (-d_1^\mu b_1^p (d_{11}^c + k_{11}^{ret\mu})$$
$$(k_{11}^- + d_{11}^c + k_{11}^{retm} + k_{11}^{ret\mu}) + k_{11}^+ b_1^m (d_{11}^c + k_{11}^{retm}) b_{11}^p + k_{11}^+ (d_{11}^c + k_{11}^{ret\mu}) b_{11}^p b_1^\mu + d_{11}^c b_1^p$$
$$\sqrt{(-4k_{11}^{+^2} b_1^m (d_{11}^c + k_{11}^{retm})(d_{11}^c + k_{11}^{ret\mu}) b_1^\mu + (k_{11}^- d_1^m d_1^\mu + k_{11}^+ b_1^m (d_{11}^c + k_{11}^{retm}) + d_1^m d_1^\mu (d_{11}^c + k_{11}^{retm} + k_{11}^{ret\mu}) + k_{11}^+ (d_{11}^c + k_{11}^{ret\mu}) b_1^\mu)^2)}$$
$$- d_1^m b_{11}^p \sqrt{(-4k_{11}^{+^2} b_1^m (d_{11}^c + k_{11}^{retm})(d_{11}^c + k_{11}^{ret\mu}) b_1^\mu + (k_{11}^- d_1^m d_1^\mu + k_{11}^+ b_1^m (d_{11}^c + k_{11}^{retm}) + d_1^m d_1^\mu (d_{11}^c + k_{11}^{retm} + k_{11}^{ret\mu}) + k_{11}^+ (d_{11}^c + k_{11}^{ret\mu}) b_1^\mu)^2)}$$
$$/(2d_1^m k_{11}^+ d_1^p (d_{11}^c + k_{11}^{retm})(d_{11}^c + k_{11}^{ret\mu}))$$

$$m = -\frac{1}{2d_1^m k_{11}^+ (d_{11}^c + k_{11}^{retm})} \left(\frac{k_{11}^- d_1^m d_1^\mu + d_1^m d_1^\mu d_{11}^c - k_{11}^+ d_{11}^c b_1^m + d_1^m d_1^\mu k_{11}^{retm} - k_{11}^+ b_1^m k_{11}^{retm} + d_1^m d_1^\mu k_{11}^{ret\mu} + k_{11}^+ d_{11}^c b_1^\mu + k_{11}^+ k_{11}^{ret\mu} b_1^\mu - }{\sqrt{(-4k_{11}^{+^2} b_1^m (d_{11}^c + k_{11}^{retm})(d_{11}^c + k_{11}^{ret\mu}) b_1^\mu + (k_{11}^- d_1^m d_1^\mu + k_{11}^+ b_1^m (d_{11}^c + k_{11}^{retm}) + d_1^m d_1^\mu (d_{11}^c + k_{11}^{retm} + k_{11}^{ret\mu}) + k_{11}^+ (d_{11}^c + k_{11}^{ret\mu}) b_1^\mu)^2} \right)$$

$$\mu_1 = -\frac{1}{2d_1^\mu k_{11}^+ (d_{11}^c + k_{11}^{ret\mu})} \left(\frac{k_{11}^- d_1^m d_1^\mu + d_1^m d_1^\mu d_{11} + k_{11}^+ d_{11}^c b_1^m + d_1^m d_1^\mu k_{11}^{retm} + k_{11}^+ b_1^m k_{11}^{retm} + d_1^m d_1^\mu k_{11}^{ret\mu} - k_{11}^+ d_{11}^c b_1^\mu - k_{11}^+ k_{11}^{ret\mu} b_1^\mu - }{\sqrt{(-4k_{11}^{+^2} b_1^m (d_{11}^c + k_{11}^{retm})(d_{11}^c + k_{11}^{ret\mu}) b_1^\mu + (k_{11}^- d_1^m d_1^\mu + k_{11}^+ b_1^m (d_{11}^c + k_{11}^{retm}) + d_1^m d_1^\mu (d_{11}^c + k_{11}^{retm} + k_{11}^{ret\mu}) + k_{11}^+ (d_{11}^c + k_{11}^{ret\mu}) b_1^\mu)^2} \right)$$

$$c_{11} = (k_{11}^- d_1^m d_1^\mu + d_1^m d_1^\mu d_{11}^c + k_{11}^+ d_{11}^c b_1^m + d_1^m d_1^\mu k_{11}^{retm} + k_{11}^+ b_1^m k_{11}^{retm} + d_1^m d_1^\mu k_{11}^{ret\mu} + k_{11}^+ d_{11}^c b_1^\mu + k_{11}^+ k_{11}^{ret\mu} b_1^\mu -$$
$$\sqrt{(-4k_{11}^{+^2} b_1^m (d_{11}^c + k_{11}^{retm})(d_{11}^c + k_{11}^{ret\mu}) b_1^\mu + (k_{11}^- d_1^m d_1^\mu + k_{11}^+ b_1^m (d_{11}^c + k_{11}^{retm}) + d_1^m d_1^\mu (d_{11}^c + k_{11}^{retm} + k_{11}^{ret\mu}) + k_{11}^+ (d_{11}^c + k_{11}^{ret\mu}) b_1^\mu)^2}))/$$
$$(2k_{11}^+ (d_{11}^c + k_{11}^{retm})(d_{11}^c + k_{11}^{ret\mu}))$$

Section S.6 Differential equations for a system of 2 miRNA interacting with 2 mRNA.

$\frac{dm_1}{dt} = b_1^m - d_1^m m_1 - k_{11}^+ m_1 \mu_1 - k_{12}^+ m_1 \mu_2 + k_{11}^- c_{11} + k_{12}^- c_{12} + k_{11}^{retm} c_{11} + k_{12}^{retm} c_{12}$
$\frac{dm_2}{dt} = b_2^m - d_2^m m_2 - k_{21}^+ m_2 \mu_1 - k_{22}^+ m_2 \mu_2 + k_{21}^- c_{21} + k_{22}^- c_{22} + k_{21}^{retm} c_{21} + k_{22}^{retm} c_{22}$
$\frac{d\mu_1}{dt} = b_1^\mu - d_1^\mu \mu_1 - k_{11}^+ m_1 \mu_1 + k_{11}^- c_{11} - k_{21}^+ m_2 \mu_1 + k_{21}^- c_{21} + k_{11}^{ret\mu} c_{11} + k_{21}^{ret\mu} c_{21} + k_{121}^- c_{112} - k_{121}^+ c_{12} \mu_1 + k_{221}^- c_{212} - k_{221}^+ c_{22} \mu_1$
$\frac{d\mu_2}{dt} = b_2^\mu - d_2^\mu \mu_2 - k_{12}^+ m_1 \mu_2 + k_{12}^- c_{12} - k_{22}^+ m_2 \mu_2 + k_{22}^- c_{22} + k_{12}^{ret\mu} c_{12} + k_{22}^{ret\mu} c_{22} + k_{112}^- c_{112} - k_{112}^+ c_{11} \mu_2 + k_{212}^- c_{212} - k_{212}^+ c_{21} \mu_2$
$\frac{dc_{11}}{dt} = k_{11}^+ m_1 \mu_1 - k_{11}^- c_{11} - k_{11}^{ret\mu} c_{11} - k_{11}^{retm} c_{11} - d_{11}^c c_{11} + k_{112}^- c_{112} - k_{112}^+ c_{11} \mu_2$
$\frac{dc_{21}}{dt} = k_{21}^+ m_2 \mu_1 - k_{21}^- c_{21} - k_{21}^{ret\mu} c_{21} - k_{21}^{retm} c_{21} - d_{21}^c c_{21} + k_{212}^- c_{212} - k_{212}^+ c_{21} \mu_2$
$\frac{dc_{12}}{dt} = k_{12}^+ m_1 \mu_2 - k_{12}^- c_{12} - k_{12}^{ret\mu} c_{12} - k_{12}^{retm} c_{12} - d_{12}^c c_{12} + k_{121}^- c_{112} - k_{121}^+ c_{12} \mu_1$
$\frac{dc_{22}}{dt} = k_{22}^+ m_2 \mu_2 - k_{22}^- c_{22} - k_{22}^{ret\mu} c_{22} - k_{22}^{retm} c_{22} - d_{22}^c c_{22} + k_{221}^- c_{212} - k_{221}^+ c_{22} \mu_1$
$\frac{dc_{112}}{dt} = k_{121}^+ c_{12} \mu_1 + k_{112}^+ c_{11} \mu_2 - (k_{121}^- + k_{112}^- + d_{112}^{'}) c_{112}$
$\frac{dc_{212}}{dt} = k_{221}^+ c_{22} \mu_1 + k_{212}^+ c_{21} \mu_2 - (k_{221}^- + k_{212}^- + d_{212}^{'}) c_{212}$
$\frac{dp_1}{dt} = b_1^p m_1 - d_1^p p_1 + b_{11}^p c_{11} + b_{12}^p c_{12} + b_{112}^p c_{112}$
$\frac{dp_2}{dt} = b_2^p m_2 - d_2^p p_2 + b_{21}^p c_{21} + b_{22}^p c_{22} + b_{212}^p c_{212}$

Section S.7 List of Chemical Reactions and species for 2miRNA-1mRNA model

1	Formation of mRNA1	Source → m_1
2	Degradation of mRNA1	m_1→Sink
3	Formation of miRNA1	Source → μ_1
4	Formation of miRNA2	Source → μ_2
5	Degradation of miRNA1	μ_1→Sink
6	Degradation of miRNA2	μ_2→Sink
7	Formation of c_{11}	m_1+ μ_1→c_{11}
8	Formation of c_{12}	m_1+ μ_2→c_{12}
9	Dissociation of c_{11}	c_{11}→ m_1+ μ_1
10	Dissociation of c_{12}	c_{12} →m_1+ μ_2
11	Degradation of c_{11}	c_{11}→ Sink
12	Degradation of c_{12}	c_{12} → Sink
13	Formation of combicomplex c_{112}	c_{11}+ μ_2→c_{112}
14	Formation of combicomplex c_{112}	c_{12}+ μ_1→c_{112}
15	Dissociation of combicomplex c_{112}	c_{112} →c_{11}+ μ_2
16	Dissociation of combicomplex c_{112}	c_{112}→ c_{12}+ μ_1
17	Degradation of combicomplex c_{112}	c_{112} → Sink
18	Return of m_1 from c_{11}	c_{11}→ m_1
19	Return of m1 from c_{11}	c_{12} → m_1
20	Return of mi1 from c_{11}	c_{11}→ mi_1
21	Return of mi2 from c_{12}	c_{12} → mi_1
22	Translation of the mrna1	m_1→p_1 +m_1
23	Degradation of protein	p_1→ Sink
24	Translation of the complex (c_{11})	c_{11} → p_1 + c_{11}
25	Translation of the complex (c_{12})	c_{12} → p_1 + c_{12}
26	Translation of the combi-complex (c_{112})	c_{112} →p_1 + c_{112}

List of Species

1	m_1	Messenger RNA1
2	μ_1, μ_2	microRNA1 and microRNA2 respectively
3	c_{11}	mRNA1 associated with miRNA1
4	c_{12}	mRNA1 associated with miRNA2
5	c_{112}	Combicomplex: m_1 associated with miRNAs 1 and 2
6	p_1	protein1

Figure S1 Slice plot showing sensitivity of protein level to miRNA formation rate for 1mRNA-1miRNA model

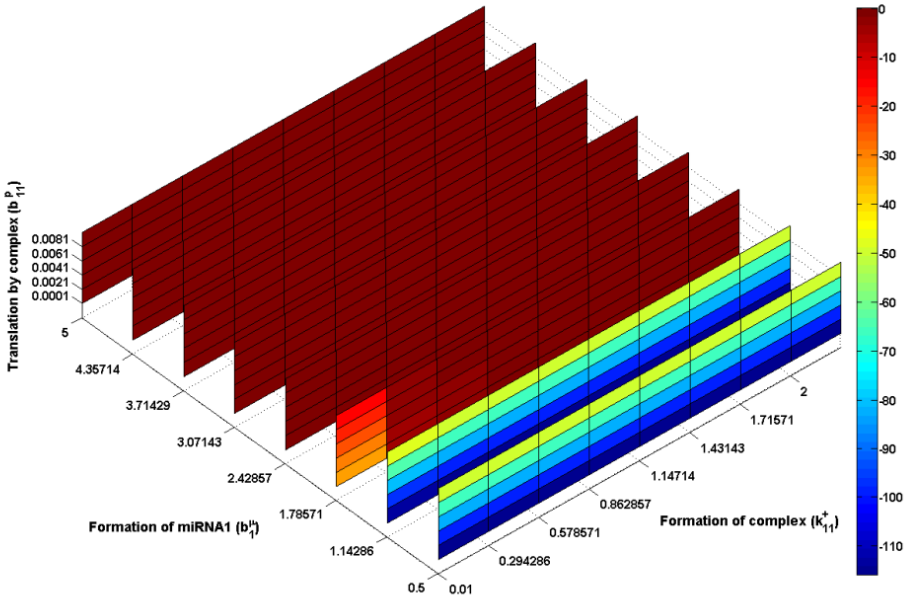

Figure S1:Slice Sensitivity plot for protein: The protein concentration of 1mRNA-1miRNA are plotted as a function of rate of formation of miRNA1(b_1^{μ}), translation by complex(c_{11}) (b_{11}^{p})and formation of complex(c_{11}) (k_{11}^{+}).The values obtained are all less than zero. This shows that at parameter that is simulated there is no region where increase in miRNA leads to rise in protein level. Other parameters listed in Table 2.

Figure S2 Slice plot showing discretized sensitivity of protein level to miRNA formation rate for 1mRNA-1miRNA model

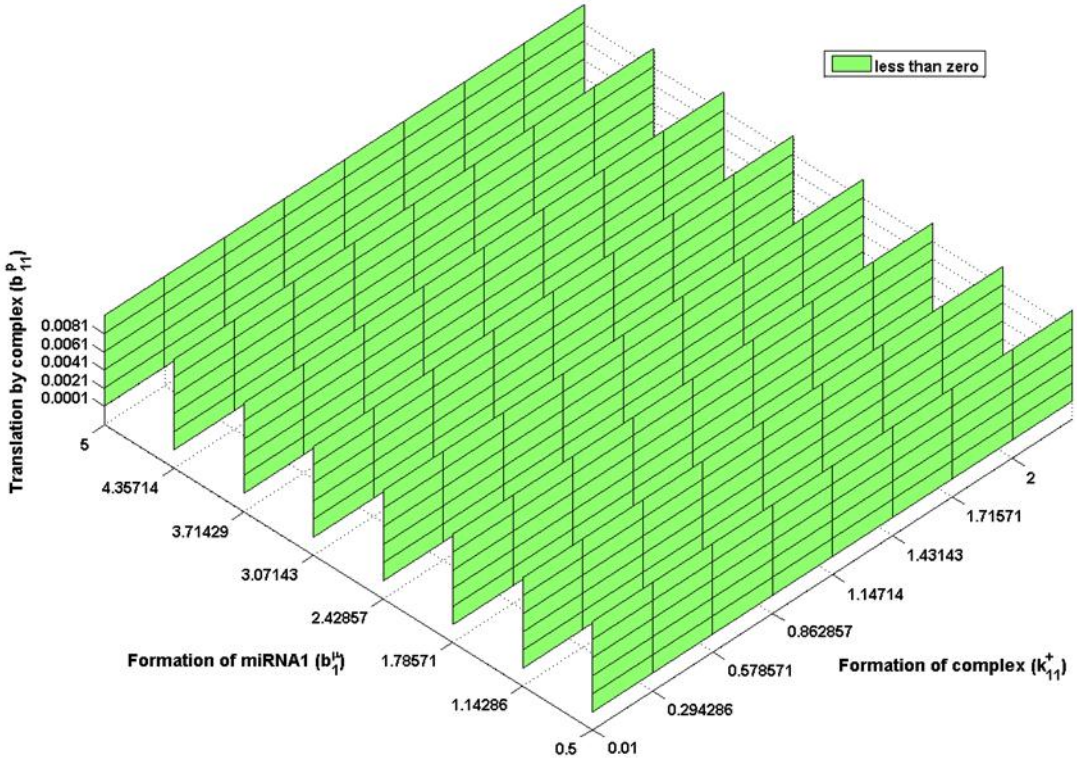

Figure S2 Discretized protein steady-state sensitivity to miRNA formation rate as a function of rate of formation of miRNA1 (b_1^{μ} molecules/sec), translation by complex(c11) (b_{11}^{p} 1/sec)and formation of complex(c11) (k_{11}^{+} molecule-1.sec-1)). Other parameters listed in Table 2.

Figure S3 Slice plot showing sensitivity as a function of translation by complex m1mi2, formation of mi2 and complex formation for 1mRNA-2 miRNA

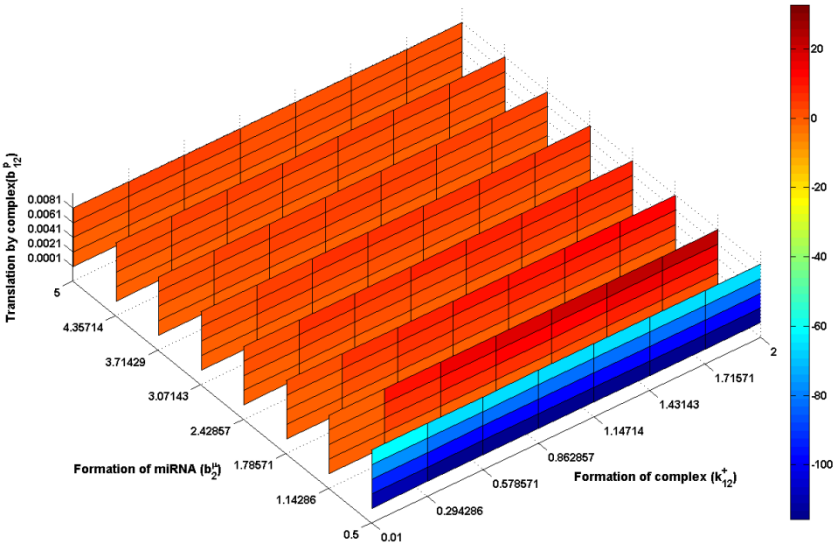

Figure S3: Slice Sensitivity plot for protein: The protein concentration of 1mRNA-2miRNA are plotted as a function of rate of formation of miRNA2(b_2^{μ}), translation by complex(c_{12}) (b_{12}^{p})and formation of complex(c_{12}) (k_{12}^{+}).The values obtained are both less than zero and more than zero. This shows that at some parameter that is simulated there is region where increase in miRNA leads to rise in protein level. Other parameters listed in Table 2.

Figure S4 Non Competitive model

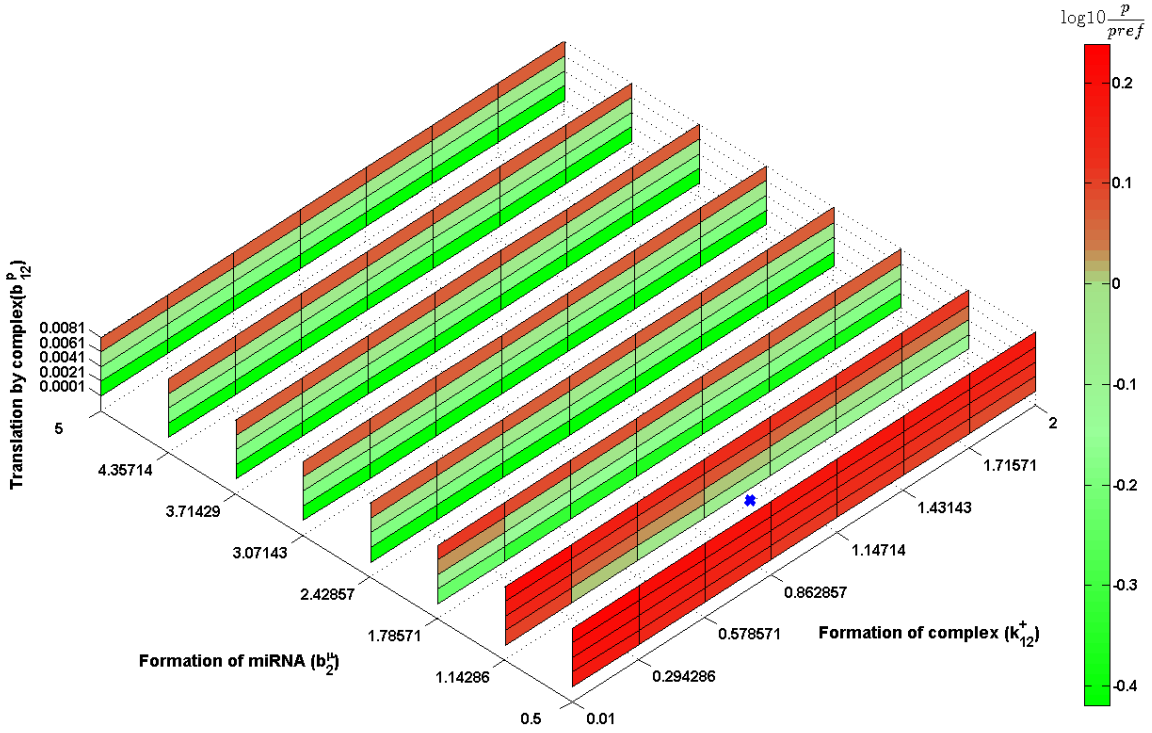

Figure S4: Slice plot for protein: Log10 (Protein steady-state ratio) plot for single mRNA- two miRNAs in non-competitive condition as a function of rate of formation of miRNA2 (b_2^{μ}), translation by complex c_{12} (b_{12}^{p}) and formation of complex c_{12} (k_{12}^{+}). Other parameters listed in Table 2. Blue colored 'x' sign is used to mark position for the reference parameter values. Log 10 protein ratio at this reference parameter value is 0.0486.

We calculate the steady-state concentrations as a function of $b_1^{\mu}, b_{11}^{p} and\ k_{11}^{+}$ keeping the other parameters constant at values as stated in Table 2 of main text.Log_{10}ratio plot for protein steady-state concentrations is obtained. We define the ratioas $\hat{p} = \frac{p}{p_{ref}}$,where p_{ref} is the protein steady-state concentration when the parameters are the 'reference' values given in Table 2 of main text. Since no analytical solution for the steady state level of target protein in case of the non-competitive interaction is obtained, sensitivity is not calculated.

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