Mathematical modelling of AIDS epidemic in India

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Mathematical and statistical models can serve as tools for understanding the epidemiology of human immunodeficiency virus and acquired immunodeficiency syndrome if they are constructed carefully. This article is meant to be an introduction to AIDS-related mathematical biology for scientists with a non-mathematical background. An applicable dynamical model is also explained.

IT was almost a decade and half ago that the first case of AIDS (Acquired Immune Deficiency Syndrome) was diagnosed in India. Initially the spread of HIV (human immunodeficiency virus) did not attract much attention in India. Only in early nineties was there a noticeable media exposure or systematic surveillance. Currently, there are 320 surveillance centers at the national level, and more than 42,000 AIDS cases were reported by the end of 2002. The current HIV estimate in India stands at about 4 million[1]. There is a lot of information on HIV viral dynamics all over the world now. Despite an identification of major risk groups and their behaviour, the picture of the dynamics of HIV spread in India is not very clear. This is primarily due to the absence of scientific means of gathering and modelling information on the infectious period of HIV infected, time to the onset of AIDS, sexual behaviour of high risk and low risk individuals in the population, probability of transmission from the infected to the susceptible per partnership and other relevant parameters.

Kermack and McKendrick's[2] treatment of the Bombay plague of 1905–06 proved the capability of mathematical models in understanding and predicting epidemics. Anderson and May[3] present more models of infections including HIV with illustrations. Models of HIV spread specific to the type of transmission have also appeared in the literature (see refs 4–7 for homosexuals and refs 4,8–10 for heterosexuals). Mathematical models have also been developed recently for other sexually transmitted diseases (STDs)[11–14]. Garnett[15] has presented a simple and useful discussion on various mathematical models for STDs.

Mukerji[16] represents one of the earliest Indian attempts at modelling data on AIDS. This model used annualized south Asian regional data and extrapolated to AIDS in future. Basu et al.[17] attempt to model the spread of AIDS in a comprehensive manner with limited data. The incu-

bation period of AIDS in India, estimated through deconvoluting HIV epidemic density and reported AIDS cases, is between 8 and 12 years[18]. Quantitative information on commercial sex activity and female commercial sex workers' (FSWs) number in India are available in various sources[19].

The complexity of the complete formalization of mathematical models is probably responsible for the discomfort with which biologists treat mathematical research literature on medicine and biology. They also appear to have reservations about the convergence between epidemiological and their mathematical models. However, there are instances of success in constructing models capable of predicting the outcome of infections. Such instances inspire our confidence in proposing realistic models. Hence present modelling attempts should be aimed at determining HIV spread mechanisms through testing the sensitivity of the assumptions. The focus of the present work is to discuss the applicability of various models to predict AIDS in India, beginning from classic simple epidemic models to more complex heterosexual transmission models proposed and back calculation method. A major portion of the main text is written in a non-mathematical language for clear understanding. Specialized terminology and relevant equations are given in the appendix for readers who wish to explore the study further. The latest models prepared for HIV spread in India are presented as explained.

Simple epidemic model

Consider an epidemic model in which the population is closed comprising susceptibles, infectives and the recovered[2]. Recovered individuals are assumed not to contribute to the infection process. But since HIV infection is not curable, this model is not applicable to it. We can modify the model by replacing the 'recovered' with the 'dead' and, still considering population as closed and is divisible into three groups, viz. X (susceptible, i.e. those at the risk of being infected with HIV), Y (infective,

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i.e. those who have HIV and can transmit it to X), and Z (the dead). If the population mixes homogeneously, then reduction in susceptibles will become increase in infectives. Infections occur at a rate proportional to the number of infectives and susceptibles, i.e. r_1XY, where r_1 is the proportionality constant. Infectives die at a rate proportional to the number of infectives, i.e. r_2Y, where r_2 is the proportionality constant. A new batch of infectives exits from the susceptible group and is added to the infective group at a given unit of time. The change in the number of infectives per unit of time will be the difference between newly turned infectives and deaths from infectives per the same unit of time. An ordinary differential equation can represent the instantaneous rate of change in each of the three variables X, Y and Z with respect to time t. See equations (1)–(3) in Appendix.

The above model does not consider advanced stage of HIV, i.e. AIDS. Our next model takes account of AIDS cases, A, but not the number of the dead. Suppose that C is the average number of sexual partners per unit time and β is the probability of transmission from infective to susceptible per partnership. Then the per capita force of infection is $\beta CXY/N$, where Y/N is the probability that the sexual partner is infective. $R_0 = \beta C/\delta$ is known as basic reproductive rate of infection, where δ is the rate of infectives moving into the AIDS group, and $1/\delta$ is the average duration from infection to AIDS. Patients die at a rate μ per unit of time. In the early stage of an epidemic, almost all the individuals in the population are susceptible, i.e. $X \cong N$; doubling time, t_d defined as the time taken for the doubling of the infected number can be calculated. The differential equations (4)–(7), and other mathematical expressions describing these are given in the Appendix.

In the case of Indian HIV epidemiology, there are only indirect estimates of incubation period, and data on the two parameters (doubling time and basic reproductive rate) discussed in the above paragraph are not available. Initial doubling time in India cannot be calculated in the absence of accurate HIV figures in the beginning of the epidemic. Current estimates of HIV cases in India are high probably because the basic reproductive rate is greater than one in the early stage of the epidemic.

Numerical examples

1. If $R_0 > 1$, then the epidemic is said to be growing and if $R_0 < 1$ then the epidemic is said to be diminishing. Assume that $R_0 = 1.034$ (i.e. just above 1) and the incubation period is 10 years. Then the doubling time (see Appendix) will be 2 years, which indicates a slow spread in the early stage. A small increase in basic reproductive rate results in the reduction of the doubling time to half of its previous value, e.g. if $R_0 = 1.069$, and incubation period 10 years, then the doubling time will be only 1 year (cf. Figure 1 also).

2. Model equations (4)–(6) (given in Appendix) can be numerically explored for suitable parameters. If $\beta = 0.02$, $C = 25$, $\delta = 0.1$ and $\mu = 1$, then the changes in the number of individuals over time will be depicted in Figure 2 *a*. Taking $\beta = 0.04$ and keeping all the parameter values as earlier, the situation changes to Figure 2 *b*. Both the figures show it of a closed population infection scenario. An increase in β can be observed in terms of faster growth in infective group as well as earlier peaking, by about six years and both of the infective and AIDS groups. The probability of transmission is a key parameter in the course of the epidemic when all other values remain constant. These values may not be representative of the true epidemic and behavioural pattern in India.

Female CSW and male HIV transmission model

In the earlier model, we assume homogeneous mixing between susceptibles and infectives, the same probability of an infective transmitting virus to a susceptible, and no factor that inhibits sex between infectives and susceptibles. To make the model realistic with respect to the behavioural changes and transmission probabilities, we need to introduce more complexity. Earlier researchers have proposed models of heterosexual behaviour[8–10]. The model presented here was based on the prevention of transmission to and from FSWs with heterogeneous mixing. Similar type of models with detailed mathematical explanation can be found elsewhere[20,21]. It explains mechanisms of transmission of virus from FSW to adult males and vice
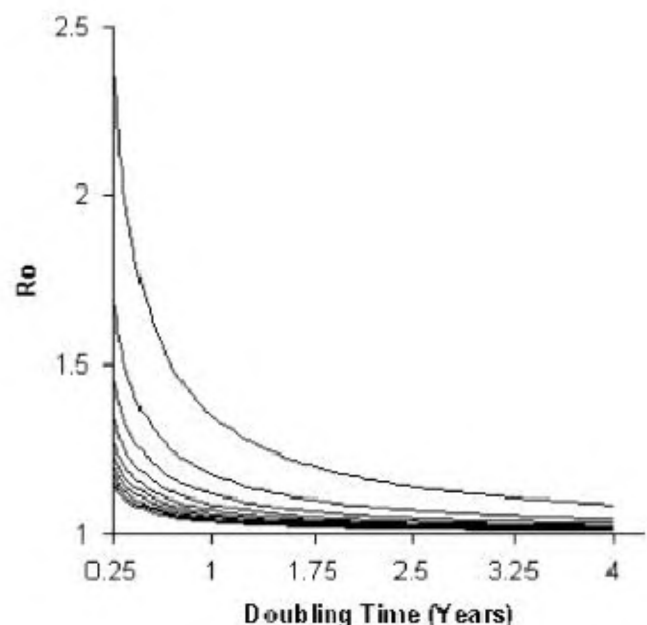

Figure 1. Basic reproductive rate. Changes in R_0 are due to variations in doubling time t_d between a quarter of a year and four years, and average incubation period δ between 2 and 20 years. $\delta = 2, 4, 6 \ldots 20$ from upper to lower curves.

versa. Figure 3 shows male susceptibles becoming HIV infective either directly or as a sequel of STDs.

Let us divide the male population that mixes with FSWs into four classes: male susceptible, HIV infective, STD infective and both STD and HIV infective (cf. Figure 2). For the purpose of this paper the rates of additions of male susceptibles from non-susceptible and STD cured are taken to be exponential. These rates in reality may be different. At the same time the number of individuals infected with HIV and STD per unit of time and the number who withdraw from risk behaviour are removed from the susceptibles. The withdrawal number is based on general withdrawal rate, or dependent on individual behaviour. In the case of males, new HIV (STD) infective population is determined from the following: *proportion* of susceptibles and HIV (STD) infected FSW population *to* the total FSW population, the *number* of partnerships per unit of time, the *probability* of transmission of HIV (STD) from an infected FSW per partnership (cf. equation (12)). After being HIV positive, one can still be STD infective and vice versa. Such individuals are called 'dual infected', i.e. with both HIV and STD. Dual-infected individuals who recover from STDs remain as HIV infective. Other withdrawal cases, e.g. natural deaths, change of risk behaviour, etc. either from HIV (STD) infective or from dual infected, can be removed from respective compartments. The Appendix lists four differential equations for changes in each class of male subpopulation (eqs (8)–(11)). Similarly, we can formulate equations for FSWs.

The probabilities of transmission are not available for Indian heterosexuals; so predictions can be based on probabilities from Ugandan data[22] (cf. ref. 23).

Rural–urban, male–female, immigration and age differentials

Introducing geographical parameters, e.g. urban and rural bases, different states, etc. in the model with a view of predicting new HIV and AIDS cases specific to them are certainly useful. Inter-state variations in sexual behaviour and condom usage have been reported. Age at first sex for urban females was low (16 years) for Bihar, and high (21 years) for Goa. For rural females it was 16 years for Andhra Pradesh, Bihar, Madhya Pradesh, Rajasthan and Uttar Pradesh and 20 years for Kerala. For urban males this was low at 19 for Madhya Pradesh and Andhra Pradesh and high at 25 years for Assam. For rural males it was low at 18 for Madhya Pradesh and high at 25 years for Kerala[1]. Reported use of condoms in all sexual encounters with non-regular sex partners in the past 12 months varied widely from 16.2 per cent in Orissa to 80.5 per cent in Goa[1]. It is not difficult to incorporate variations such as behavioural changes, condom usage and features like immigration rate in the model and corresponding

software for predictions. The net immigration will be negligible in predictions for India, but not for metropolitan cities in India. Besides, since incubation period of AIDS is dependent on the age at the time of infection, some models incorporated that factor in their projections. Though, male–female behavioural patterns might change with increasing age, incubation period is not gender-biased. These factors need to be incorporated while modelling age-specific impact of HIV/AIDS in India.
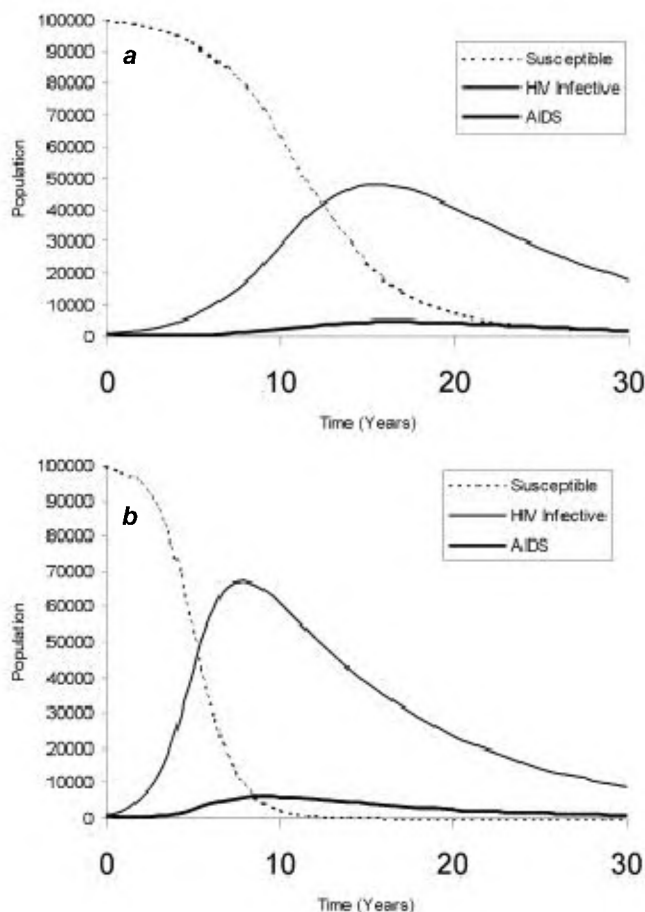

Figure 2. (*a*) $\beta = 0.02$, $C = 25$, $\delta = 0.1$ and $\mu = 1$; (*b*) $\beta = 0.02$, $C = 25$, $\delta = 0.1$ and $\mu = 1$, in the model equations (4) to (6).
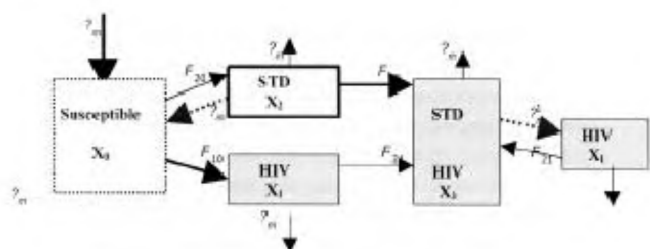

Figure 3. Schematic diagram of male susceptible acquiring STD and HIV from FSWs. λ_m is entry rate into male susceptible compartment, F_{10}, F_{20}, F_{21}, F_{12}, are four coefficients of movements from respective compartments as shown above in the figure. γ_m and γ_m^l are recovery rates from STD representing *without* and *with* HIV infection. μ_m is mortality rate (see Appendix for further details).

Back calculation method

Back calculation method requires accurate number of reported AIDS cases over each calendar year for several years and an estimate of incubation period distribution of AIDS. Incubation period of AIDS, T, could be taken as the duration between the time of HIV infection, ξ, and the time of diagnosis of AIDS, ψ. Using a basic relation among these three quantities of time, the cumulative number of AIDS at time t can be estimated as a convolution of HIV incidence density and incubation distribution of AIDS[24,25] (eq. (13), Appendix). Rao and Srivenkataramana explained the limitations of this method for the Indian data[26]. This method can also be used to estimate incubation distribution[18] through Newton's method of maximization for the likelihood equation. These authors assume parametric distributions for ξ and ψ, and perform deconvolution to obtain distribution of T. Deconvolution method can also be performed, for e.g. through FFT (Fast Fourier Transformations). Historically, Weibull distribution gave good fit for the US data[27,28]. It was also applied for the Indian type data[29,30]. An example of incubation distribution obtained through deconvolution using Indian HIV density and AIDS data is shown in Figure 4. This graph is useful in understanding the proportion of the HIV-infected who developed full-blown AIDS over time.

The reliability of this method rests on the accuracy and completeness of reported AIDS cases. In case of incomplete reported data is applied, a provision for under-reporting has to be made. Still, unlike the models explained earlier, the back calculation method requires only very few parameters to predict AIDS. So this happens to be the most widely used to estimate HIV prevalence from AIDS incidence number[31]. This method does not suggest any specific strategy intervention for policy formulations.

Discussion

The selection of models dealt with here was motivated by the general nature of HIV in India and dynamical model-
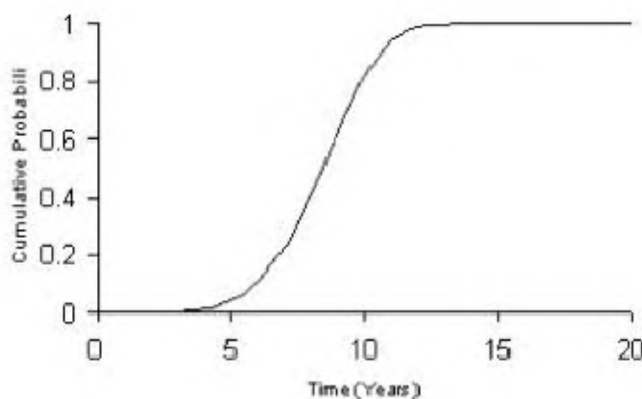

Figure 4. Weibull distribution $(1 - \alpha \exp(- t/\beta))$ was plotted using earlier estimated values of $\alpha = 9.0131$, $\beta = 5.2193$ for the Indian data[18].

ling initiatives, and is not by a desire to present a comprehensive account of mathematical models available till date. There is an urgent need for extensive mathematical models of AIDS incidence and spread[32] so as to enable informed and efficient investments in preventive therapeutic measures. This article concentrates on models of spread.

From an epidemiological perspective, R_0 is an important indicator of the initial course of HIV. In the case of homogeneous mixing, it stands as a formula by using which one can calculate any one of the three parameters, viz. basic reproductive rate, doubling time of infection in an early stage and incubation period of AIDS if the other two parameters are known. In the simple model, susceptible becomes infective following sexual interaction with an infective. However, there is a probability per partnership attached to the transmission of the virus to a susceptible, which this model fails to incorporate. The latter model accommodates the probability of transmission as well as a new category of AIDS individuals. In addition, death rates among the infected also vary on the basis of whether deaths occur from AIDS or non-AIDS causes. Now, the model becomes capable of explaining the deaths those are not due to full-blown AIDS (see (14)–(18) in the Appendix). But, if we assume that all the infective classes that do not develop AIDS will remain infectious indefinitely, then the model becomes again simple. We can introduce stochastic component instead of a deterministic one. However, it is traditional to see mathematical models for the spread of AIDS to take a deterministic form. Besides, this form can lead to approximation to stochastic moments. Obtaining explicit solutions using stochastic models is more difficult than obtaining through deterministic forms. For more discussion see refs 33, 34.

Basic reproductive rate and doubling time in the early stage of the epidemic affect the shape of the growth curve[4]. Though all the required parameters for the complex heterosexual model explained earlier may not be available for India, the model can be thoroughly tested for its sensitivity to behavioural parameters. The model tries to explain the extent of male infections by heterosexual rather than homosexual behaviour. In case of FSW-driven sexual behaviour in India, these models can contribute to the planning of preventive procedures. Behavioural parameters can also help public health planning. For example, the number of sex partners per unit of time, which is multiplier in obtaining coefficients of movement from one compartment to another, causes fluctuations in the number of new STD and HIV infections. This model concentrates on the spread mechanisms by excluding incubation period data in its equations. However, considering the rate of development of AIDS and transmission probability parameters based on the severity can accommodate complexity. Mathematical modelling of HIV data in India can be attained more economically by using transmission probabilities that are available from African data instead of searching for transmission probabilities for each infec-

tion stage within India. Observing how other parameters like recovery from STD and rate of withdrawal from sexual activity lead to reduction in the spread of HIV are useful for policy framing.

The back calculation method is a powerful tool to reconstruct HIV incidence using AIDS incidence over several years. Because the incubation period is naturally long and variable, most of the recent AIDS incidence observed need not be affected by recent HIV trends in the population. In other words, a decline in HIV incidence in recent years will not be captured by the latest AIDS incidence. Sometimes this epidemiological feature may encourage drawing wrong conclusions unless results are interpreted carefully. Incubation period could be different for IVD (intra venous drug) users than for the heterosexual population. Weibull distribution approximately suits the incubation period because of its nature as discussed above.

More complex and micro-simulation models could be prepared for predicting AIDS. However, in the present Indian setup, there is a need to build macro-level models. Sexual partnership studies, surveys of usage of condoms in general as well as among HIV-infected individuals, and studies of the sharing of needles between infective and susceptible will enhance modelling accuracies in India. Understanding the models alone will not reduce or control the spread of HIV in India. We ought to generate reliable data for compact modelling purposes. This paper has the primary purpose of promoting a formal modelling culture among health planners and survey designers in a way that would help them cope with the complexity of HIV in India.

Appendix

Terminology and differential equations

This section contains four subsections and some of the terminology may be common between these subsections.

Simple epidemiological models

X : No. susceptible to HIV
Y : No. of HIV infective
Z : No. of deaths from HIV
A : No. of AIDS cases
 : $N_1 = X + Y + A$
r_1, r_2 : Constants of proportionality
β : Probability of transmission from infective to susceptible
C : No. of partners per unit of time
$1/\delta$: Average incubation period of AIDS
μ : Rate of death among AIDS cases

$$\frac{dX}{dt} = -r_1 XY \tag{1}$$

$$\frac{dY}{dt} = r_1 XY - r_2 Y \tag{2}$$

$$\frac{dZ}{dt} = r_2 Y \tag{3}$$

$$\frac{dX}{dt} = -\frac{\beta CXY}{N_1} \tag{4}$$

$$\frac{dY}{dt} = \frac{\beta CXY}{N_1} - \delta Y \tag{5}$$

$$\frac{dA}{dt} = \delta Y - \mu A \tag{6}$$

$$t_d = \frac{1}{\delta(R_0 - 1)} \bullet(2). \tag{7}$$

Female CSW and male HIV transmission model

Part of the terminology for this model is explained in Figure 2.

β_{10} : HIV transmission probability from FSW to a susceptible male
β_{20} : STD transmission probability from FSW to a susceptible male
β_{21} : HIV transmission probability from a FSW with both STD and HIV
δ_1, δ_2 : Withdrawal rate of males due to the reasons other than sexual activity

$$\frac{dX_0}{dt} = \lambda_{\lrcorner} - (F_{10} + F_{20} + \mu_{\lrcorner})X_0 + \gamma_m X_2 \tag{8}$$

$$\frac{dX_1}{dt} = F_{10}X_0 - (\mu_m + \delta_1 + F_{21})X_1 + \gamma_{\lrcorner}^1 X_3 \tag{9}$$

$$\frac{dX_2}{dt} = F_{20}X_0 - (\mu_{\lrcorner} + \delta_2 + F_{12})X_2 - \gamma_{\lrcorner} X_2 \tag{10}$$

$$\frac{dX_3}{dt} = F_{21}X_1 + F_{12}X_2 - (\mu_{\lrcorner} + \delta_1 + \delta_2)X_3 - \gamma_{\lrcorner}^1 X_3 \tag{11}$$

$$F_{ij} = \beta_{ij} C \left[\frac{Y_i + Y_j}{\sum_{k=0}^{3} Y_k} \right] \{i = 1, 2; j = 0, 1, 2\}. \tag{12}$$

Other coefficients are calculated in a similar way. Y_i's ($i = 0, 1, 2, 3$) are FSW counterpart of the male compartments explained in Figure 3. For the sake of simplicity, I have omitted differential equations representing male to female FSW transmission dynamics.

Back calculation method

If Φ (t) is the incubation distribution at time t, ψ (t) is the cumulative number of AIDS cases up to time t, ξ (x) is HIV incidence density.

$$\Psi(t) = \int_0^t \xi(x)\Phi(t-x)\_\mathbf{\downarrow}. \tag{13}$$

Modified simple epidemic model

Y_1 : No. of individuals who develop AIDS after HIV infection

Y_2 : No. of individuals who do not develop AIDS after HIV infection

A_1 : No. of AIDS cases developed

A_2 : No. of non-AIDS cases

p_1 : Probability of developing AIDS after HIV infection

p_2 : Probability of developing AIDS after HIV infection

$1/\delta_1$: Average incubation period of AIDS

$1/\delta_2$: Average period of infectiousness in case of non-development of AIDS

μ_1 : Rate of death for AIDS cases

μ_2 : Rate of death for non-AIDS cases

$N = X + Y_1 + Y_2 + A_1 + A_2$

$$\frac{dX}{dt} = \frac{-\beta CX}{N} \tag{14}$$

$$\frac{dY_1}{dt} = \frac{p_1\beta CX}{N} - \delta_1 Y_1 \tag{15}$$

$$\frac{dY_2}{dt} = \frac{p_2\beta CX}{N} - \delta_2 Y_2 \tag{16}$$

$$\frac{dA_1}{dt} = \delta_1 Y_1 - \mu_1 A_1 \tag{17}$$

$$\frac{dA_2}{dt} = \delta_2 Y_2 - \mu_2 A_2. \tag{18}$$

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